

Supplementary Data

A metal-free and mild approach to 1,3,4-oxadiazol-2(3*H*)-ones via oxidative C-C bond cleavage using molecular oxygen

Bumhee Lim,^{a†} Seunggun Park, ^{a†} Jae Hyun Park,^a Jongsik Gam,^b Sanghee Kim,^a

Jung Woon Yang,^c and Jeeyeon Lee ^{a*}

^a. College of Pharmacy, Research Institute of Pharmaceutical sciences, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Korea

^b. Department of Medicinal Bioscience, College of Interdisciplinary & Creative Studies, Konyang University, 121 Daehak-ro, Nonsan, Chungnam, Korea

^c. Department of Energy Science, Sungkyunkwan University, Suwon 16419, South Korea

* Corresponding author

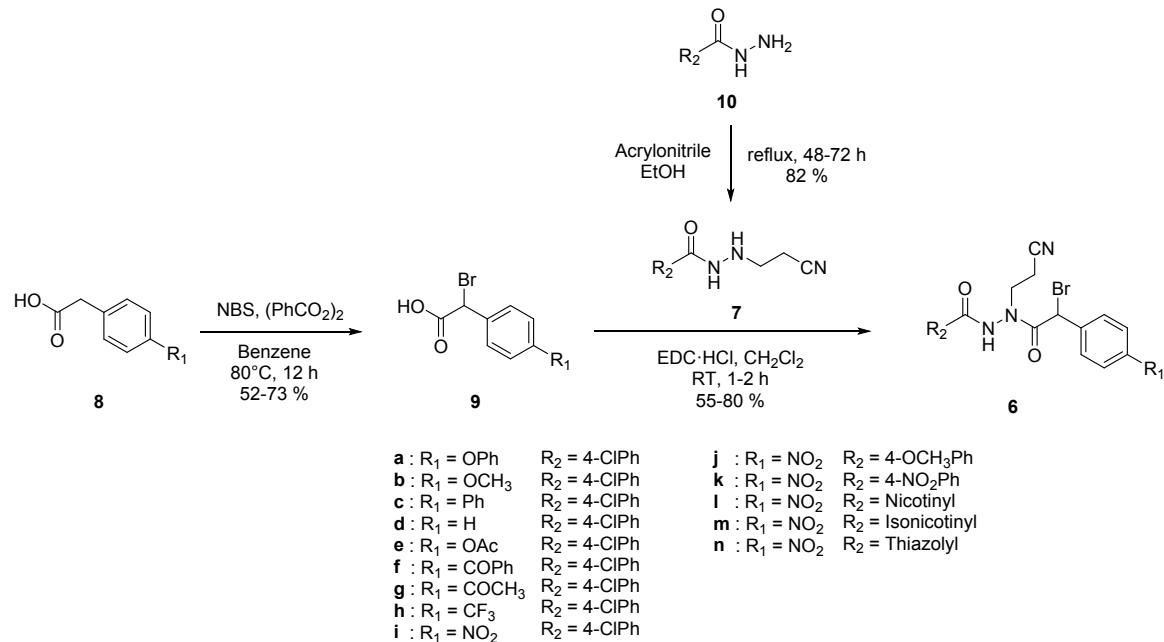
Tel.: +82 2 880 2471; fax: + 82 2 884 8334; e-mail: jyleeut@snu.ac.kr

Table of Contents

I. Synthesis	S3 – S24
1. General synthetic procedure for 6a and 6c-6n	S3 – S8
2. ^1H - and ^{13}C -NMR spectra	S9 – S24
II. Supporting Data	S25 – S28
Figure S1. Quantitative TLC analyses demonstrating a reaction progress suppressed by TEMPO.	
	S25
Figure S2. ^1H -NMR analysis of the reaction mixture in the presence or absence of K_2CO_3 .	
	S26
Figure S3. ^1H -NMR analysis of the reaction mixture of the cyclization products from 6 .	
	S27
Figure S4. Progress of the spontaneous cyclization reaction of 6a to 3a without K_2CO_3 .	
	S28
III. Single crystal x-ray crystallographic data	S29 – S37

I. Synthesis

1. General synthetic procedure for **6a** and **6c-6n**



Scheme S1. Synthesis of **6a** and **6c-6n**.

To a stirred solution of α -bromophenylacetic acid **9** (1.0 mmol) and *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 1.5 mmol) in 10 mL of CH₂Cl₂, compound **7** (1.0 mmol) was added. The reaction mixture was allowed to stir at room temperature until complete conversion was observed by TLC. The reaction mixture was washed with brine (10 mL) and the organic layers were dried over anhydrous sodium sulfate and concentrated to give the crude product, which was further purified by flash chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford the compound **6**.

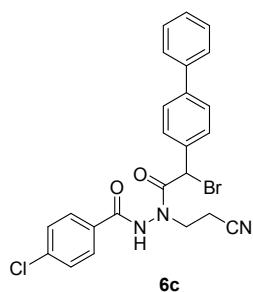
N'-(2-bromo-2-(4-phenoxyphenyl)acetyl)-4-chloro-*N'*-(2-cyanoethyl)benzohydrazide (**6a**).

6a

2-bromo -2-(4-phenoxyphenyl)acetic acid (**9a**, 307 mg, 1.00 mmol) was reacted for 1 h according to the general procedure described above to yield **6a** (309 mg, 60%) as a bright yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 8.28 (bs, 1H, -CONH), 7.77*/7.71 (2 \times d, J = 8.7 / 8.4 Hz, 2H), 7.50 (dd, J_1 = 8.1 Hz, J_2 = 6.0 Hz, 2H), 7.41-7.30 (m, 4H), 7.15 (t, J = 7.5 Hz, 1H), 7.01

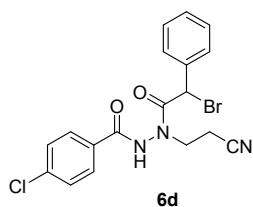
(dd, $J_1 = 7.5$ Hz, $J_2 = 122$ Hz, 2H), 6.97-6.92 (m, 2H), 5.58 (s, 1H), 3.99 (bs, 2H), 2.80 (bs, 2H); ^{13}C -NMR (75 MHz, CDCl_3): 169.7, 164.8, 164.7*, 158.4, 156.1, 139.8, 130.5, 129.9 (2C), 128.8 (2C), 129.4 (2C), 128.9 (2C), 128.1 (2C), 124.1, 119.7, 118.5 (2C), 118.4, 46.1, 43.4, 16.3 *represents the isomer

***N'*-(2-([1,1'-biphenyl]-4-yl)-2-bromoacetyl)-4-chloro-*N'*-(2-cyanoethyl)benzohydrazide (6c).**



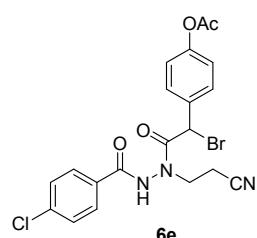
2-([1,1'-biphenyl]-4-yl)-2-bromoacetic acid (**9c**, 495 mg, 1.70 mmol) was reacted for 2 h according to the general procedure to yield **6c** (383 mg, 45%) as a bright yellow oil. ^1H -NMR (600 MHz, CDCl_3): δ 7.75*/7.70 (bs / d, $J = 7.3$ Hz, 2H), 7.56-7.53 (m, 4H), 7.49-7.40 (m, 6H), 7.36 (t, $J = 7.3$ Hz, 1H), 5.66 (s, 1H), 3.96 (bs, 2H), 2.76 (bs, 2H); ^{13}C -NMR (150 MHz, CDCl_3): 169.7, 164.7, 142.3, 142.2*, 139.9*, 139.8, 129.5, 129.4 (4C), 128.9, 128.89 (2C), 128.87 (2C), 128.8*, 128.5, 127.8, 127.6*, 127.1 (4C), 118.4, 46.25, 46.24, 16.3, 16.2*; HR-MS (FAB+): m/z calcd for $\text{C}_{24}\text{H}_{20}\text{BrClN}_3\text{O}_2$ [$\text{M}+\text{H}]^+$: 496.0427, found: 496.0421 *represents the isomer

***N'*-(2-bromo-2-phenylacetyl)-4-chloro-*N'*-(2-cyanoethyl)benzohydrazide (6d).**



2-bromo-2-phenyl acetic acid (**9d**, 713 mg, 3.32 mmol) was reacted for 2 h according to the general procedure to yield **6d** (710 mg, 51%) as a bright yellow oil. ^1H -NMR (500 MHz, CDCl_3): δ 9.01 (bs, 1H, -CONH), 7.70*/7.66 (2 \times d, $J = 6.5$ / 8.0 Hz, 2H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.37-7.36 (m, 1H), 7.31-7.29 (m, 4H), 5.67 (s, 1H), 3.95 (bs, 2H), 2.87 (bs, 2H); ^{13}C -NMR (125 MHz, CDCl_3): 169.9, 164.9, 164.8*, 139.7, 129.4 (2C), 129.3 (2C), 129.0 (2C), 128.9 (2C), 128.8, 128.7, 128.0, 118.5, 118.4*, 46.08, 46.07, 16.3, 16.2*; HR-MS (FAB+): m/z calcd for $\text{C}_{18}\text{H}_{16}\text{BrClN}_3\text{O}_2$ [$\text{M}+\text{H}]^+$: 420.0114, found: 420.0111 *represents the isomer

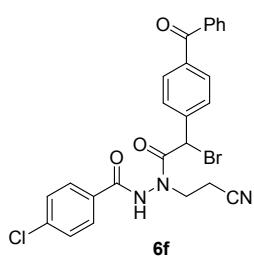
4-(1-bromo-2-(2-(4-chlorobenzoyl)-1-(2-cyanoethyl)hydrazinyl)-2-oxoethyl) phenyl acetate (6e).



2-(4-acetoxyphenyl)-2-bromoacetic acid (**9e**, 732 mg, 2.68 mmol) was reacted for 2 h according to the general procedure to yield **6e** (744 mg, 58%) as a bright yellow oil. ^1H -NMR (600 MHz, CDCl_3): δ 8.61 (bs, 1H, -

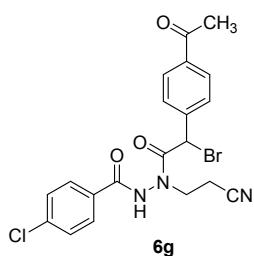
CONH), 7.72*/ 7.67 (bs / d, $J = 7.4$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.35 (d, $J = 8.7$ Hz, 2H), 7.05 (d, $J = 8.7$ Hz, 2H), 5.56 (s, 1H), 3.94 (bs, 2H), 2.74 (bs, 2H), 2.28 (s, 3H); ^{13}C -NMR (150 MHz, CDCl_3): 169.5 (2C), 164.9, 151.3, 139.9, 129.6, 129.5 (4C), 129.02, 129.0 (4C), 118.5, 46.5 (2C), 21.2, 16.4, 16.3*; HR-MS (FAB+): m/z calcd for $\text{C}_{20}\text{H}_{18}\text{BrClN}_3\text{O}_4$ [$\text{M}+\text{H}]^+$: 478.0169, found: 478.0169 *represents the isomer

***N'*-(2-(4-benzoylphenyl)-2-bromoacetyl)-4-chloro-*N'*-(2-cyanoethyl)benzohydrazide (6f).**



2-(4-benzoylphenyl)-2-bromoacetic acid (**9f**, 500 mg, 1.57 mmol) was reacted for 2 h according to the general procedure to yield **6f** (353 mg, 43%) as a bright yellow oil. ^1H -NMR (800 MHz, CDCl_3): δ 9.41 (bs, 1H, -CONH), 7.77 (bs, 2H), 7.69 (d, $J = 7.7$ Hz, 2H), 7.67 (d, $J = 8.2$ Hz, 2H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.46-7.42 (m, 6H), 5.72 (s, 1H), 4.20 (bs, 1H), 3.66 (bs, 1H), 2.82 (bs, 2H); ^{13}C -NMR (200 MHz, CDCl_3): δ 196.4, 169.4, 165.08*, 165.03, 139.8, 138.1, 138.0, 136.8, 133.0, 130.4, 130.1 (2C), 129.4 (4C), 129.0 (4C), 128.4 (2C), 118.3, 45.9, 45.8, 16.3, 16.2*; HR-MS (FAB+): m/z calcd for $\text{C}_{25}\text{H}_{20}\text{BrClN}_3\text{O}_3$ [$\text{M}+\text{H}]^+$: 524.0377, found: 524.0378 *represents the isomer

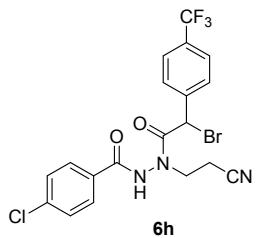
***N'*-(2-(4-acetylphenyl)-2-bromoacetyl)-4-chloro-*N'*-(2-cyanoethyl)benzohydrazide (6g).**



2-(4-acetylphenyl)-2-bromoacetic acid (**9g**, 800 mg, 3.12 mmol) was reacted for 2 h according to the general procedure to yield **6g** (515 mg, 36%) as a colorless oil. ^1H -NMR (300 MHz, CD_3OD): δ 8.00-7.89 (m, 2H), 7.81 (d, $J = 8.8$ Hz, 2H), 7.56-7.53 (m, 4H), 5.97 (s, 1H), 4.14 (bs, 1H), 3.74 (bs, 1H), 2.79 (bs, 2H), 2.58 (s, 3H); ^{13}C -NMR (75 MHz, CD_3OD): δ 200.5, 172.1, 171.8, 140.9, 132.0, 131.6 (4C), 130.7 (4C), 130.6 (2C), 120.0, 41.2 (2C), 27.1, 17.5; HR-MS (FAB+): m/z calcd for $\text{C}_{20}\text{H}_{18}\text{BrClN}_3\text{O}_3$ [$\text{M}+\text{H}]^+$: 462.0220, found: 462.0209 *represents the isomer

***N'*-(2-bromo-2-(4-(trifluoromethyl)phenyl)acetyl)-4-chloro-*N'*-(2-cyanoethyl)benzohydrazide (6h).**

2-bromo-2-(4-(trifluoromethyl)phenyl)acetic acid (**9h**, 800 mg, 2.83 mmol) was reacted for 2 h according to the general procedure to yield **6h** (807 mg, 59%) as a bright yellow oil. ^1H -NMR (800



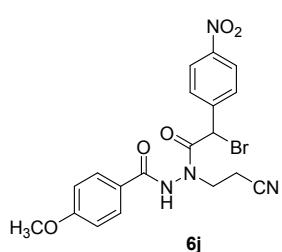
MHz, CDCl₃): δ 9.13 (bs, 1H, -CONH), 7.73-7.70 (bd, 2H), 7.55-7.54 (m, 2H), 7.52-7.51 (m, 2H), 7.47-7.44 (m, 2H), 5.65 /5.62* (s / bs, 1H). 4.26 (bs, 1H), 3.58 (bs, 1H), 2.87-2.70 (bm, 2H); ¹³C-NMR (200 MHz, CDCl₃): δ 169.6, 165.0*, 164.9, 140.0, 139.9, 131.3 (dq, *J*₁ = 63.4 Hz, *J*₂ = 130.2 Hz), 129.5 (2C), 129.4 (2C), 128.93 (2C), 128.88 (2C), 128.5, 123.6 (q, *J* = 270.7 Hz). 118.55, 118.54*, 46.0, 45.9, 16.3, 16.2*; HR-MS (FAB+): *m/z* calcd for C₁₉H₁₅BrClF₃N₃O₂ [M+H]⁺: 487.9988, found: 487.9996 *represents the isomer

***N'*-(2-bromo-2-(4-nitrophenyl)acetyl)-4-chloro-*N'*-(2-cyanoethyl)benzohydrazide (6i).**

2-bromo-2-(4-nitrophenyl)acetic acid (**9i**, 516 mg, 2.31 mmol) was reacted for 2 h according to the general procedure to yield **6i** (619 mg, 58%) as a colorless oil. ¹H-NMR (300 MHz, CD₃OD): δ 8.30-8.13 (bd, 2H), 7.86-7.79 (m, 2H), 7.74-7.64 (bm, 2H), 7.57-7.53 (m, 2H), 6.03 (s, 1H), 4.13 (bs, 1H), 3.78 (bs, 1H), 2.78 (t, *J* = 6.4 Hz, 2H); ¹³C-NMR (75 MHz, CD₃OD): δ 171.5, 168.7, 150.2, 141.0, 132.3, 131.46 (2C), 131.42 (2C), 130.9 (4C), 125.3, 120.0, 47.2, 44.7, 17.47, 17.44*; HR-MS (FAB+): *m/z* calcd for C₁₈H₁₅BrClN₄O₄ [M+H]⁺: 464.9965, found: 464.9952

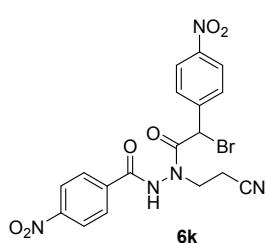
*represents the isomer

***N'*-(2-bromo-2-(4-nitrophenyl)acetyl)-*N'*-(2-cyanoethyl)-4-methoxybenzohydrazide (6j).**



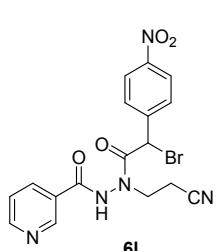
N'-(2-cyanoethyl)-4-methoxybenzohydrazide (**7j**, 56 mg, 0.26 mmol) and 2-bromo-2-(4-nitrophenyl)acetic acid (**9j**, 66 mg, 0.26 mmol) were reacted for 16 h according to the general procedure to yield **6j** (43 mg, 36%) as a colorless oil. ¹H-NMR (800 MHz, CDCl₃): δ 8.79 (bs, 1H), 8.16 (d, *J* = 8.6 Hz, 2H), 7.77 (bs, 2H), 7.56 (d, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.66 (s, 1H), 4.26 (bs, 1H), 3.87 (s, 3H), 3.63 (bs, 1H), 2.86 (bs, 1H), 2.68 (bs, 1H); ¹³C-NMR (200 MHz, CDCl₃): 176.3, 169.4*, 165.5, 163.8, 148.1, 129.5 (2C), 129.2 (2C), 128.7, 126.5 (2C), 122.2, 118.4, 114.5 (2C), 55.6, 46.4, 28.4, 16.3. *represents the isomer

***N'*-(2-bromo-2-(4-nitrophenyl)acetyl)-*N'*-(2-cyanoethyl)-4-nitrobenzohydrazide (6k).**



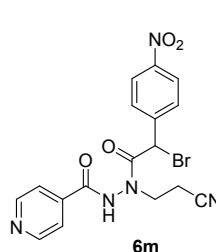
N'-(2-cyanoethyl)-4-nitrobenzohydrazide (**7k**, 80 mg, 0.34 mmol) and 2-bromo-2-(4-nitrophenyl)acetic acid (**9k**, 89 mg, 0.34 mmol) were reacted for 2 h according to the general procedure to yield **6k** (69 mg, 43%) as a bright yellow oil. ¹H-NMR (800 MHz, DMSO-*d*₆): δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 6.47 (s, 1H), 4.10-4.03 (m, 2H), 3.01 (td, *J* = 6.4, 1.7 Hz, 2H); ¹³C-NMR (200 MHz, DMSO-*d*₆): 158.8, 148.9, 148.0, 145.9, 141.4, 134.7, 128.8 (2C), 127.7 (2C), 124.0 (2C), 123.9 (2C), 118.8, 75.5, 54.9, 15.9.

***N'*-(2-bromo-2-(4-nitrophenyl)acetyl)-*N'*-(2-cyanoethyl)nicotinohydrazide (6l).**



N'-(2-cyanoethyl)nicotinohydrazide (**7l**, 110 mg, 0.58 mmol) and 2-bromo-2-(4-nitrophenyl)acetic acid (**9l**, 150 mg, 0.58 mmol) were reacted for 16 h according to the general procedure to yield **6l** (107 mg, 43%) as a colorless oil. ¹H-NMR (800 MHz, CD₃OD): δ 9.02* / 8.99 (bs / bs, 1H), 8.76 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.28* / 8.25 (d / d, *J* = 8.2 / 7.9 Hz, 2H), 8.15 (d, *J* = 5.4 Hz, 1H), 7.72* / 7.65 (bs / bs, 2H), 7.61-7.59 (m, 1H), 6.08 (s, 1H), 4.14 (bs, 1H), 3.80 (bs, 1H), 2.81 (bs, 2H); ¹³C-NMR (200 MHz, CD₃OD): 171.6, 171.4*, 167.6, 154.6 (2C), 154.5*, 150.3 (2C), 138.5, 138.4, 131.7, 131.3, 126.1 (2C), 125.3, 120.0, 57.0, 46.9, 17.5. *represents the isomer

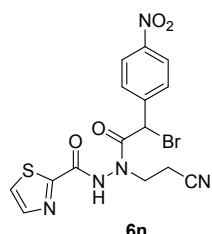
***N'*-(2-bromo-2-(4-nitrophenyl)acetyl)-*N'*-(2-cyanoethyl)isonicotinohydrazide (6m).**



N'-(2-cyanoethyl)isonicotinohydrazide (**7m**, 110 mg, 0.58 mmol) and 2-bromo-2-(4-nitrophenyl)acetic acid (**9m**, 150 mg, 0.58 mmol) were reacted for 16 h according to the general procedure to yield **6m** (128 mg, 51%) as a colorless oil. ¹H-NMR (800 MHz, CD₃OD): δ 8.76-8.75 (m, 2H), 8.24* / 8.12 (bs / d, *J* = 8.7 Hz, 2H), 7.83 / 7.70* (d / bs, *J* = 6.0 Hz, 2H), 7.78 (d, *J* = 6.1 Hz, 2H), 7.64* / 7.43 (bs / d, *J* = 8.9 Hz, 2H), 6.07 (s, 1H), 4.14 (bs, 1H), 3.81 (bs, 1H), 2.80 (t, *J* = 6.6 Hz, 2H); ¹³C-NMR (200 MHz, CD₃OD): 174.9, 171.5*, 167.6, 167.5*, 152.1 (2C), 149.2, 144.3, 141.8, 132.7 (2C),

152.2 (2C), 124.0 (2C), 120.3*, 120.1, 46.2, 40.5, 17.7*, 17.5. *represents the isomer

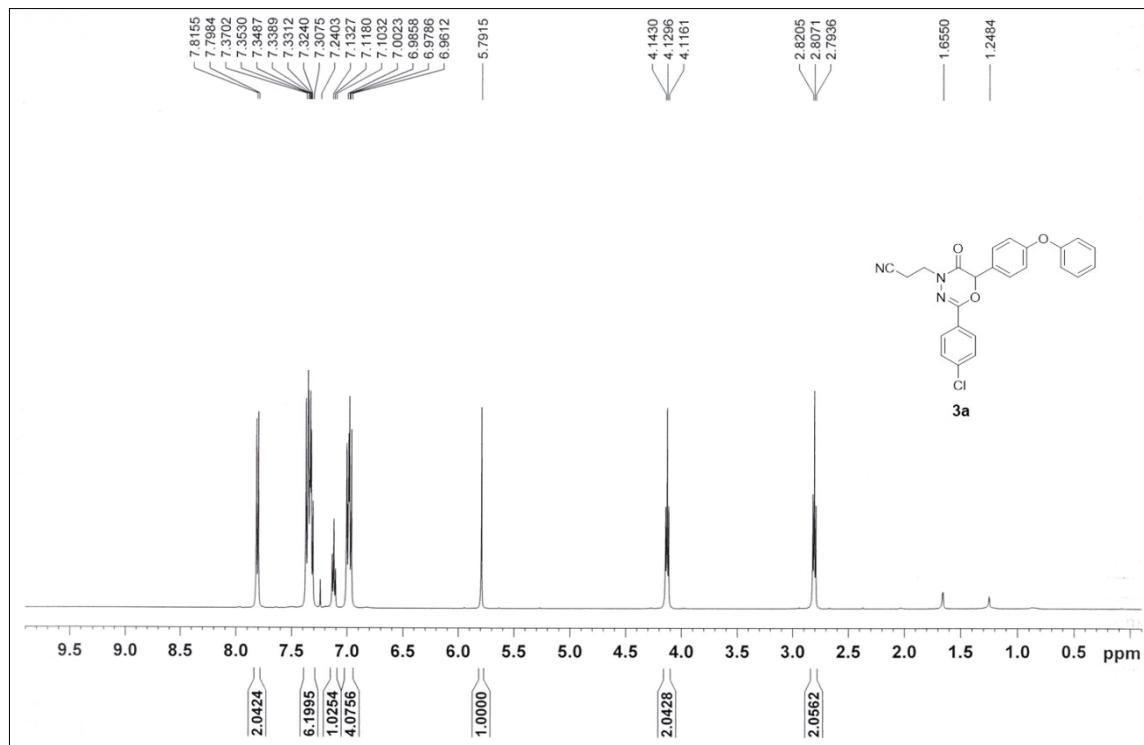
***N'*-(2-bromo-2-(4-nitrophenyl)acetyl)-*N'*-(2-cyanoethyl)thiazole-2-carbohydrazide (6n).**



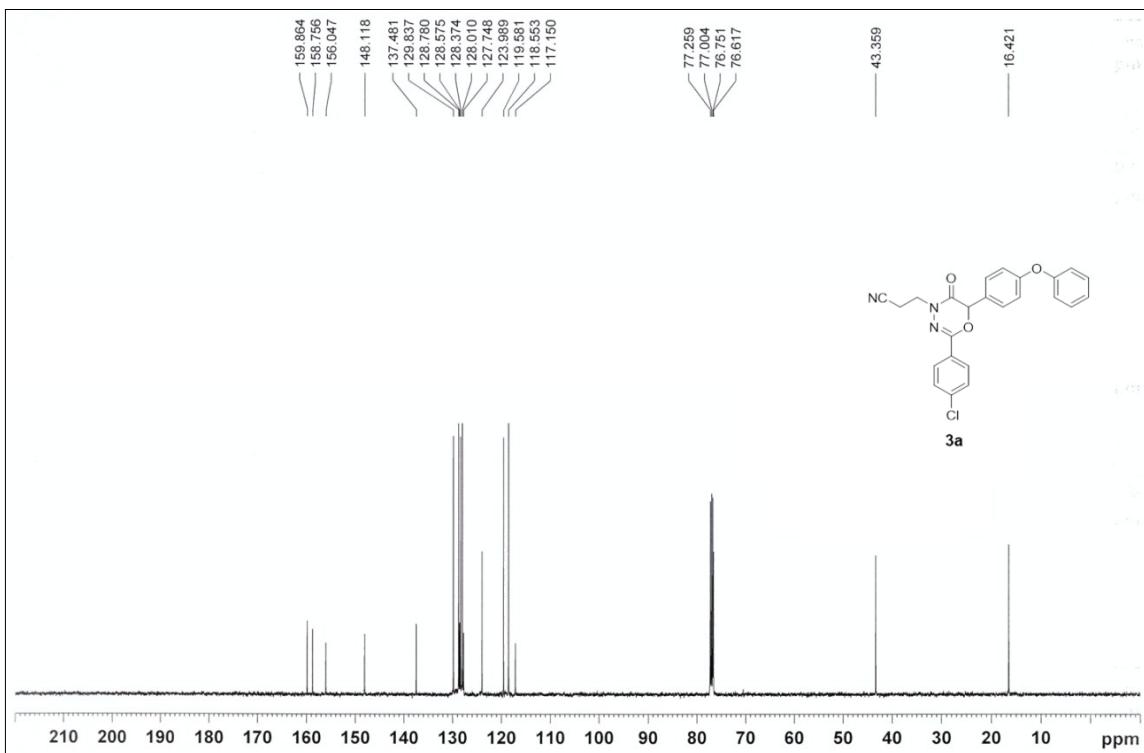
N'-(2-cyanoethyl)thiazole-2-carbohydrazide (**7n**, 48 mg, 0.26 mmol) and 2-bromo-2-(4-nitrophenyl)acetic acid (**9n**, 69 mg, 0.26 mmol) were reacted for 2 h according to the general procedure to yield **6n** (69 mg, 33%) as a colorless oil. ¹H-NMR (800 MHz, CDCl₃): δ 9.35 (bs, 1H), 8.17 (d, *J* = 8.6 Hz, 2H), 7.98 (d, *J* = 2.8 Hz, 1H), 7.76 (d, *J* = 2.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 5.67 (s, 1H), 4.02 (bs, 1H), 3.94 (bs, 1H), 2.80 (bs, 1H), 2.76 (bs, 1H); ¹³C-NMR (200 MHz, CDCl₃): 168.6, 159.0, 158.2, 148.2, 144.6 (2C), 141.5, 129.3, 126.8 (2C), 123.9, 117.4, 77.2, 46.6, 16.2.

2. ^1H - and ^{13}C -NMR spectra

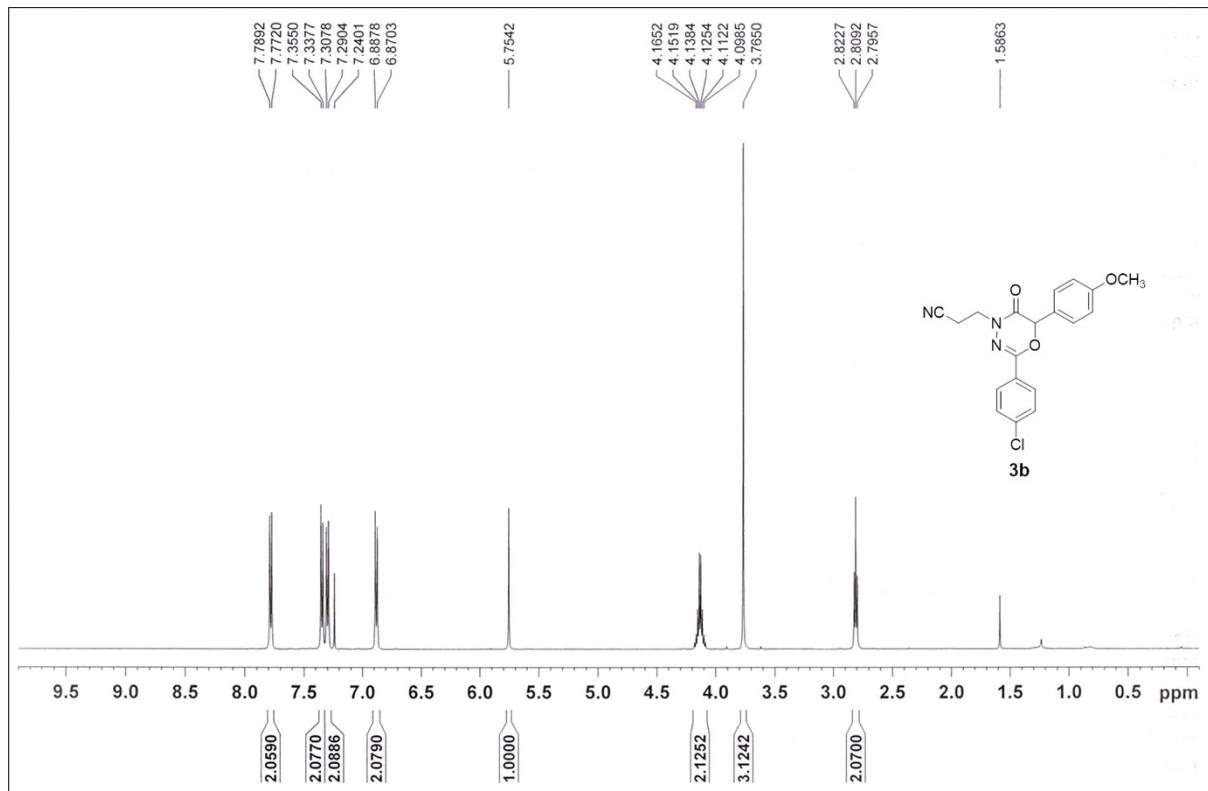
^1H -NMR of compound **3a** (500 MHz, CDCl_3)



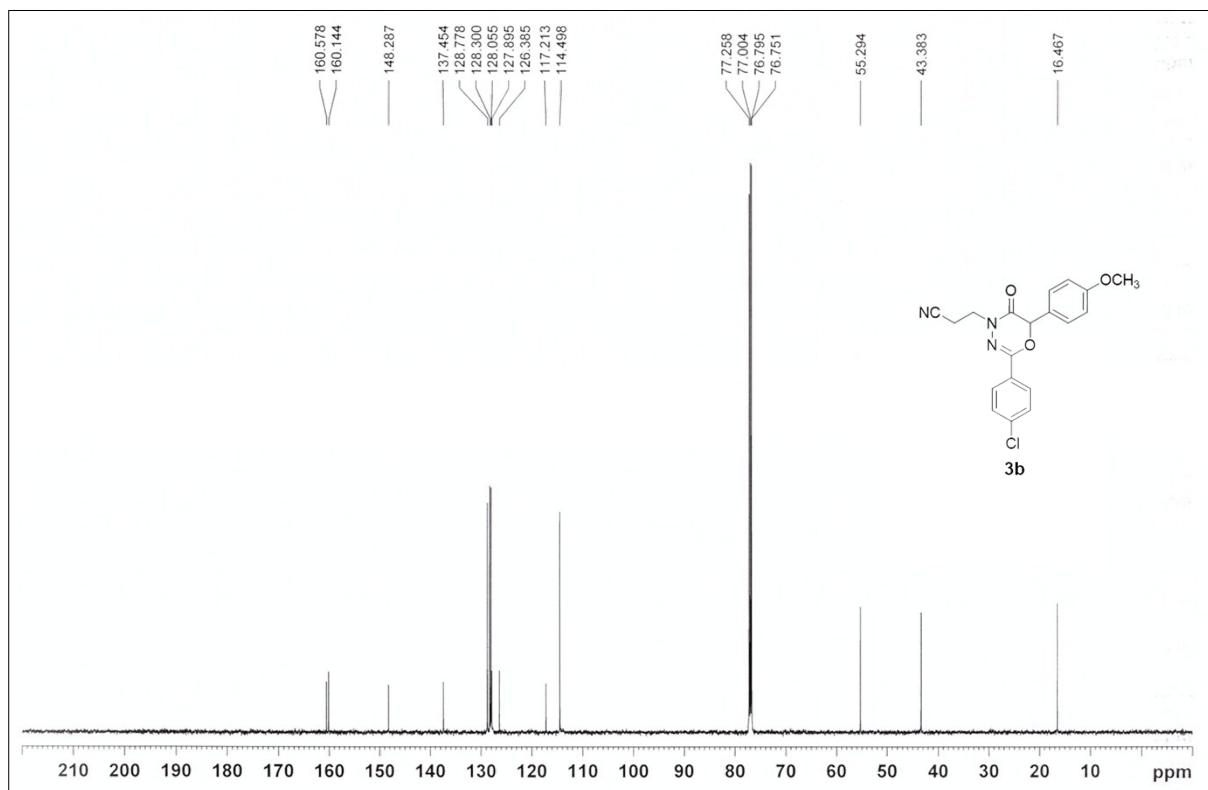
^{13}C -NMR of compound **3a** (125 MHz, CDCl_3)



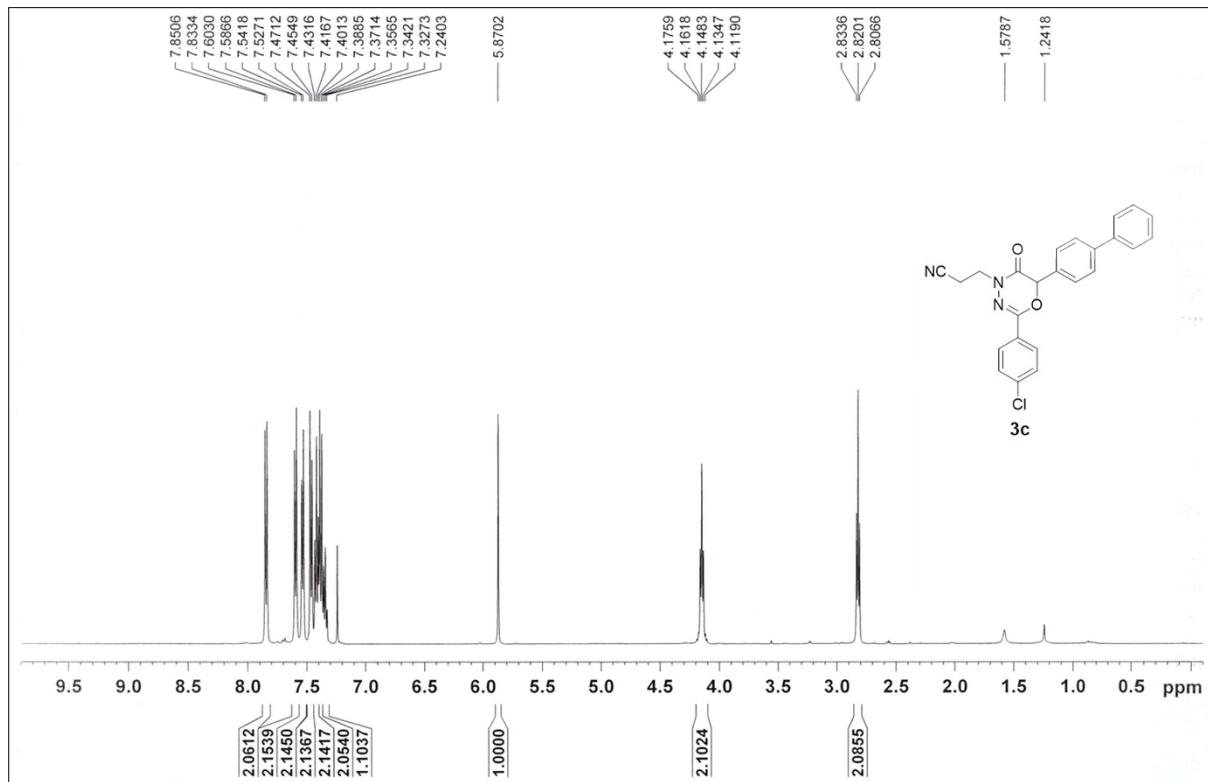
¹H-NMR of compound **3b** (500 MHz, CDCl₃)



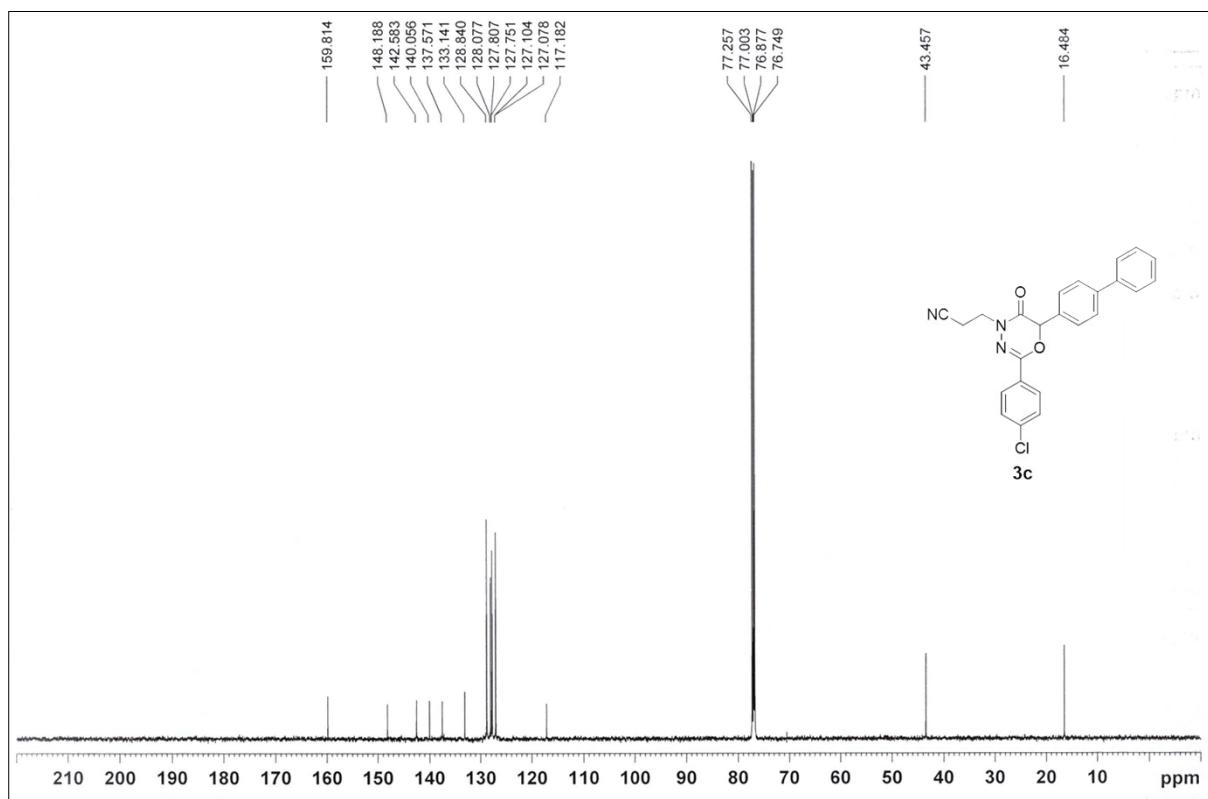
¹³C-NMR of compound **3b** (125 MHz, CDCl₃)



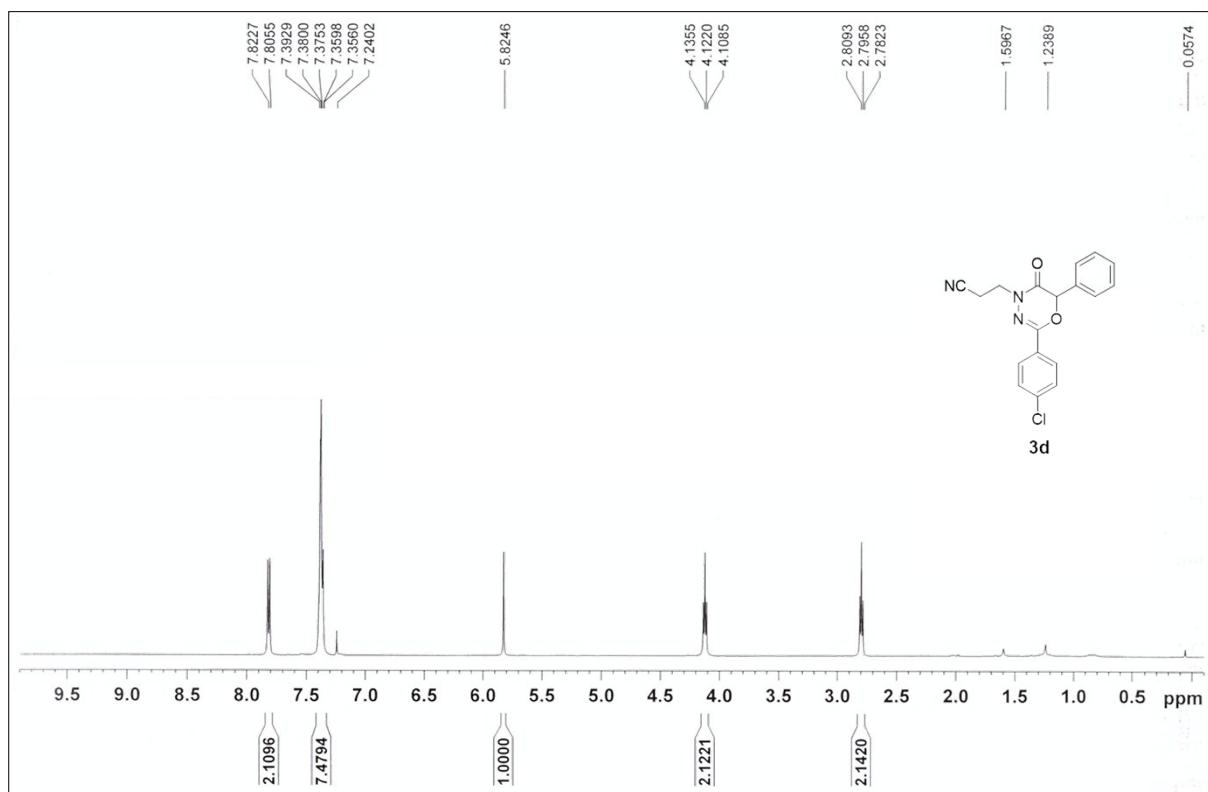
¹H-NMR of compound **3c** (500 MHz, CDCl₃)



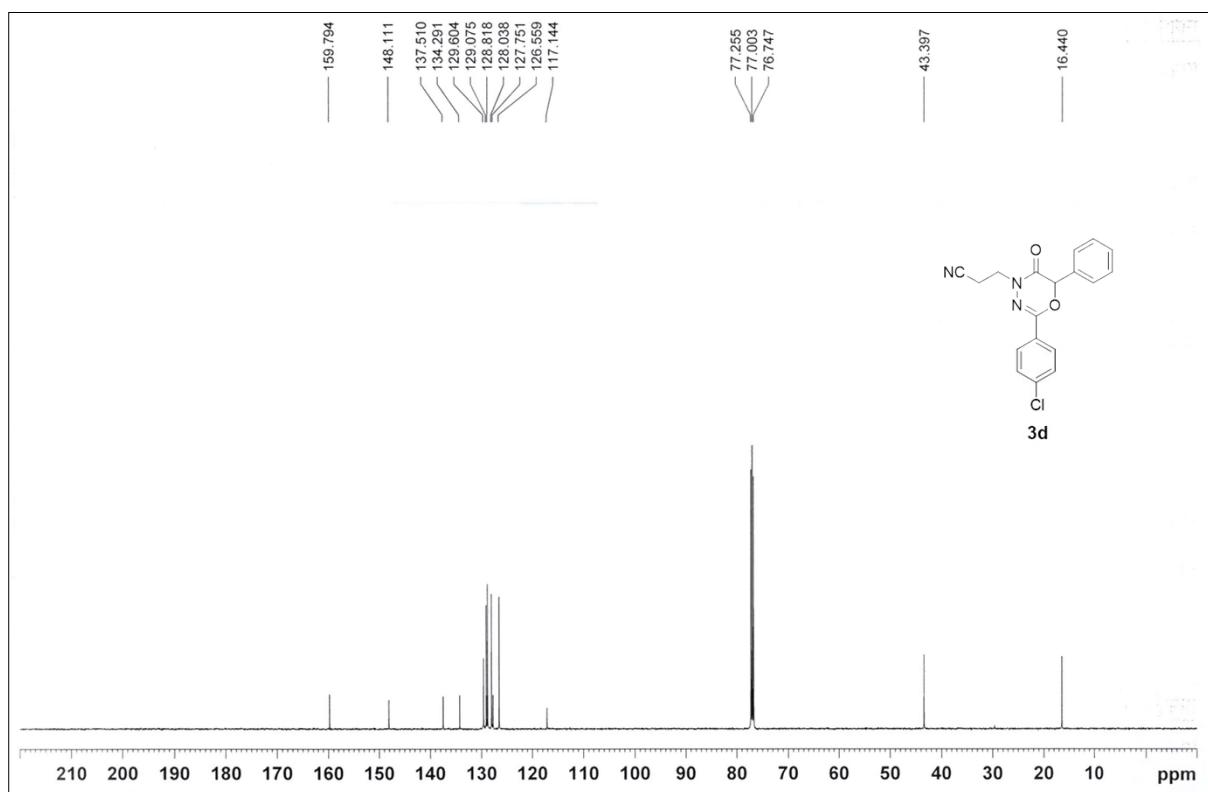
¹³C-NMR of compound **3c** (125 MHz, CDCl₃)



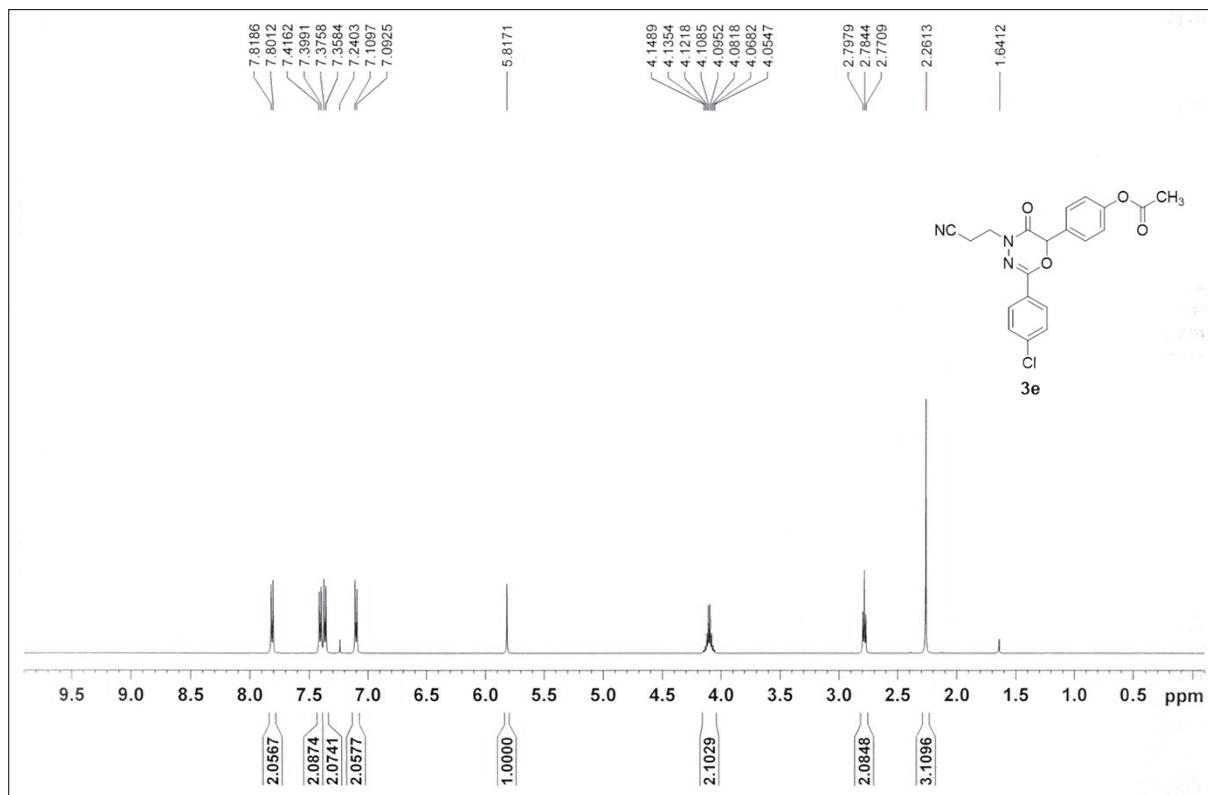
¹H-NMR of compound **3d** (500 MHz, CDCl₃)



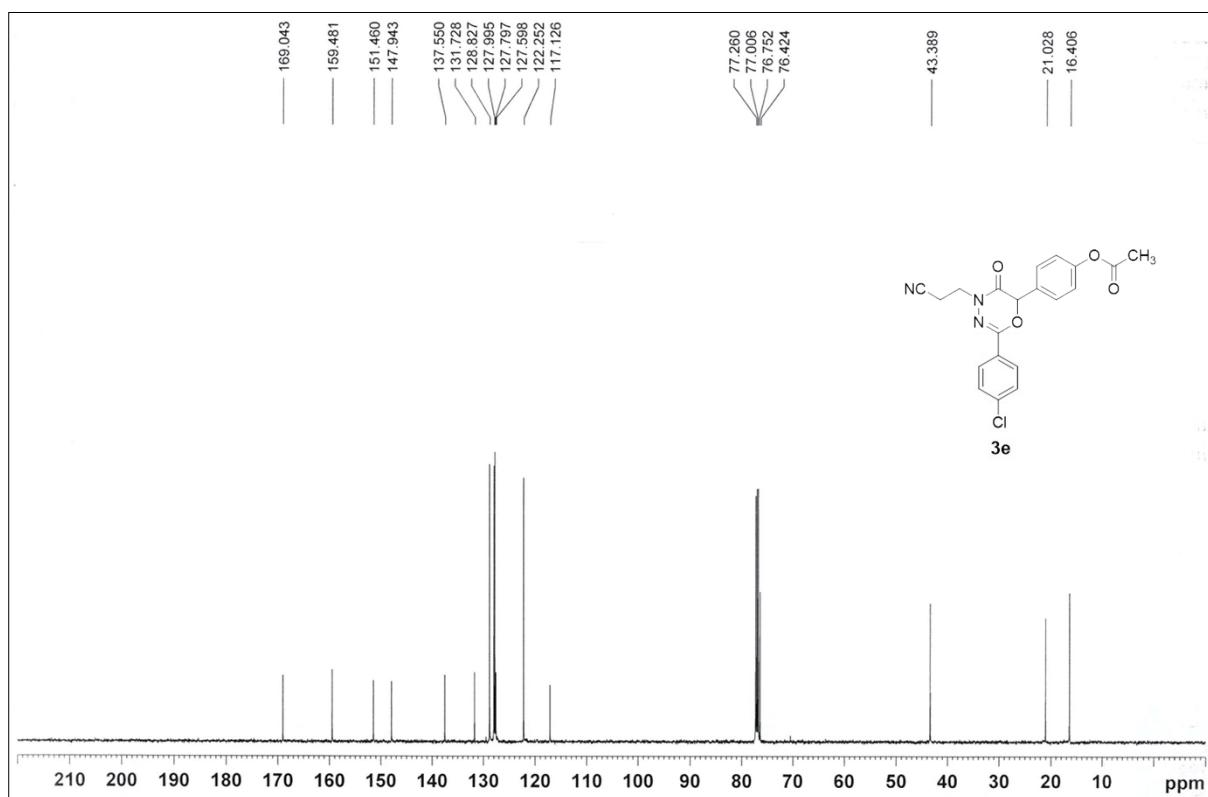
¹³C-NMR of compound **3d** (125 MHz, CDCl₃)



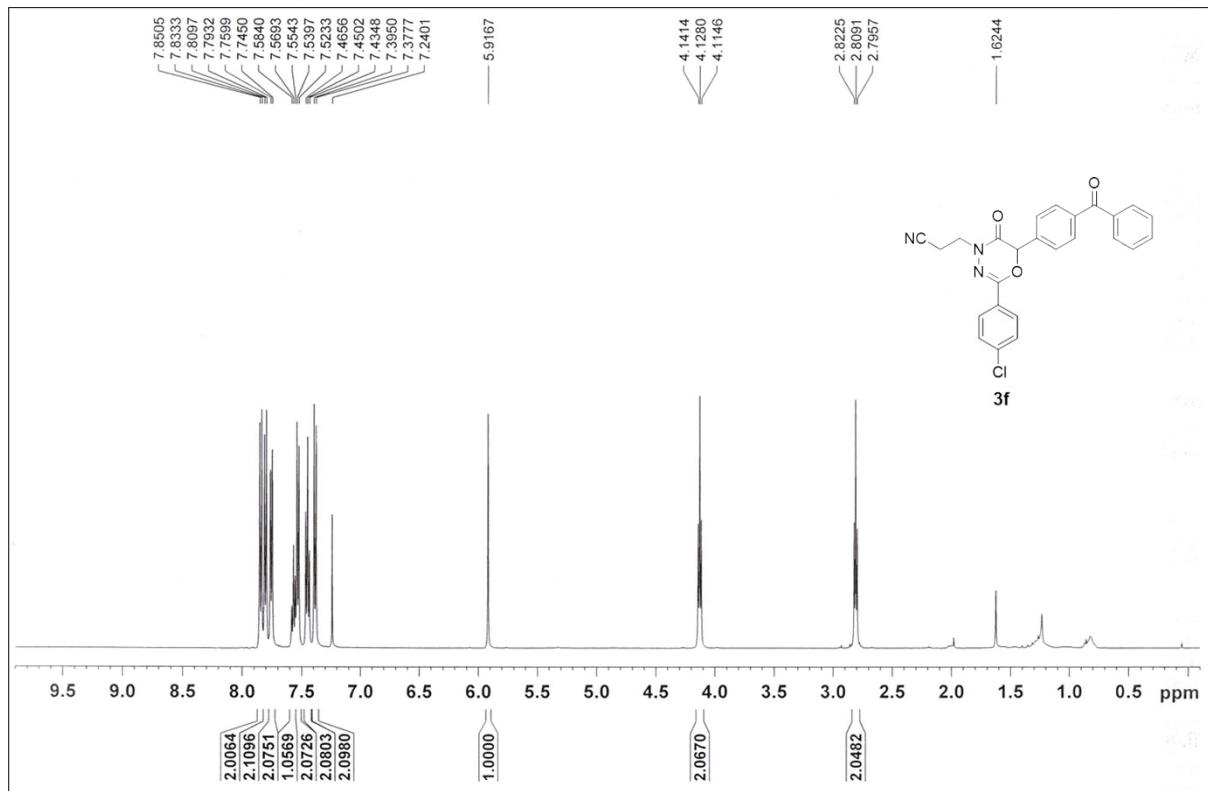
¹H-NMR of compound 3e (500 MHz, CDCl₃)



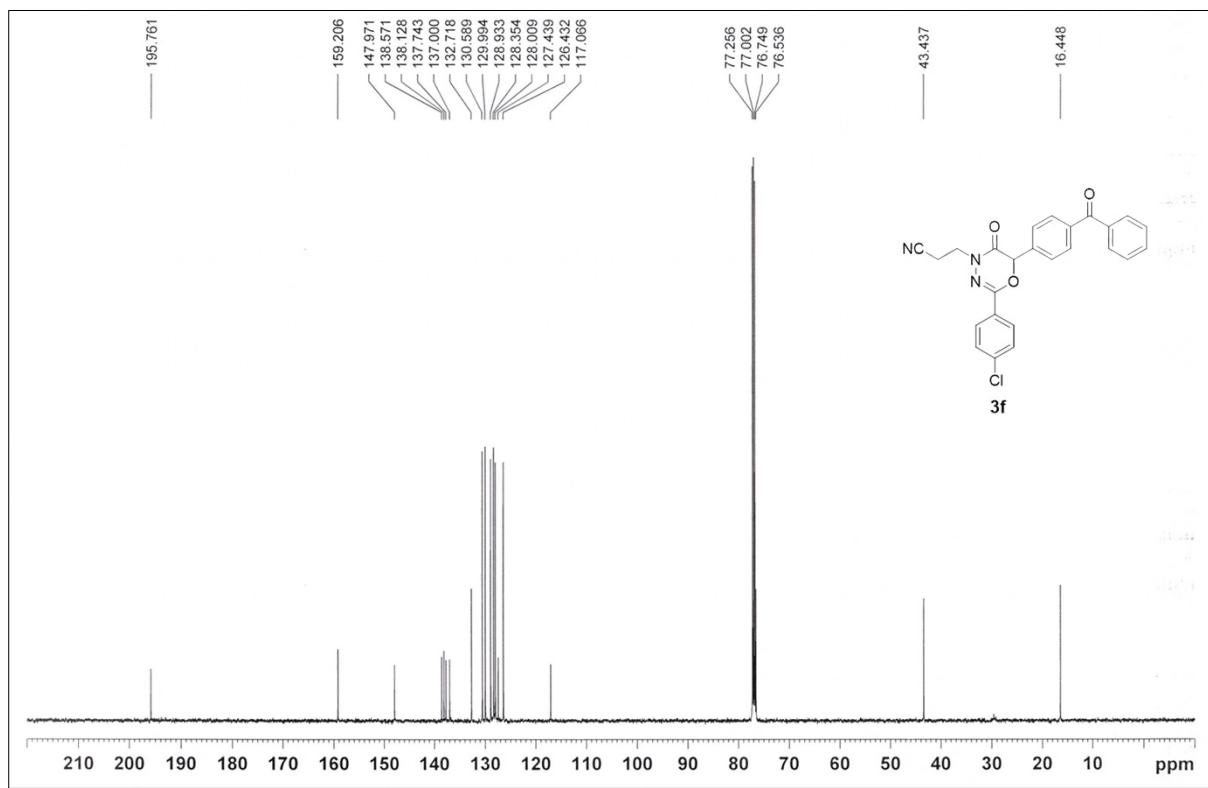
¹³C-NMR of compound 3e (125 MHz, CDCl₃)



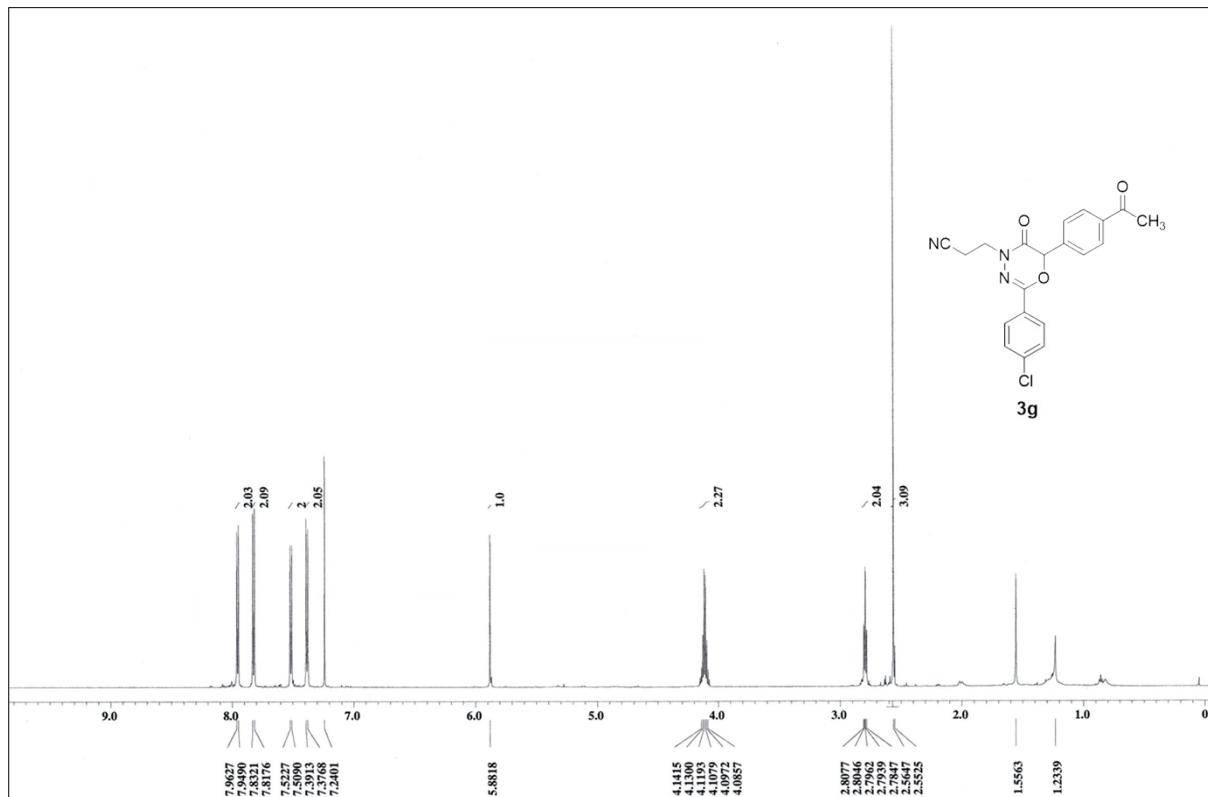
¹H-NMR of compound **3f** (500 MHz, CDCl₃)



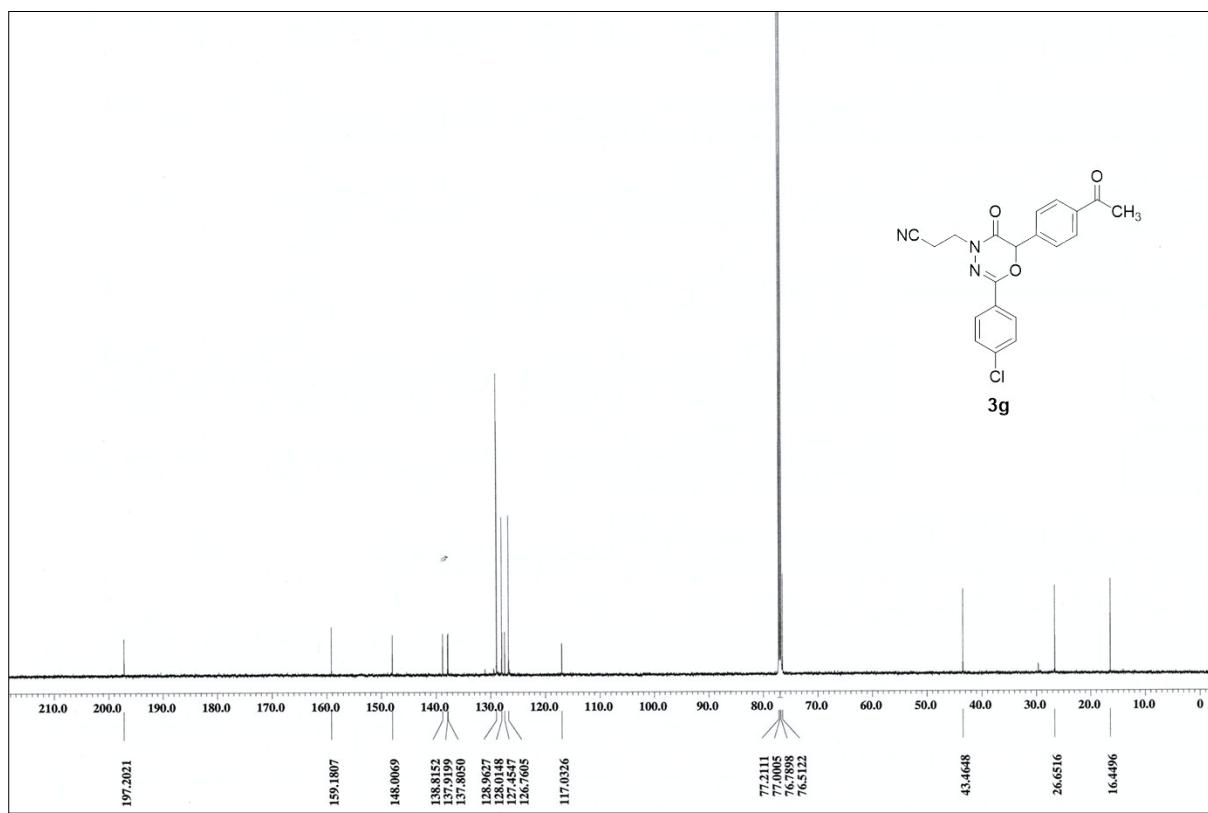
¹³C-NMR of compound **3f** (125 MHz, CDCl₃)



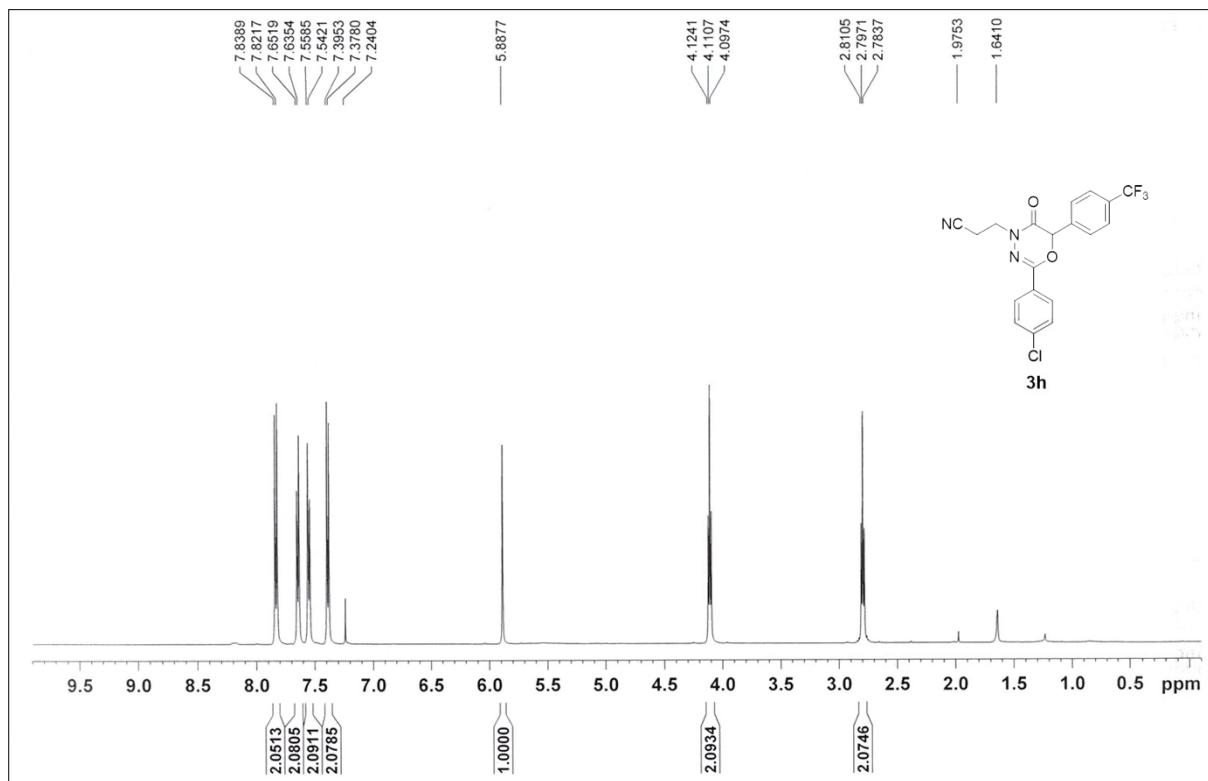
¹H-NMR of compound **3g** (600 MHz, CDCl₃)



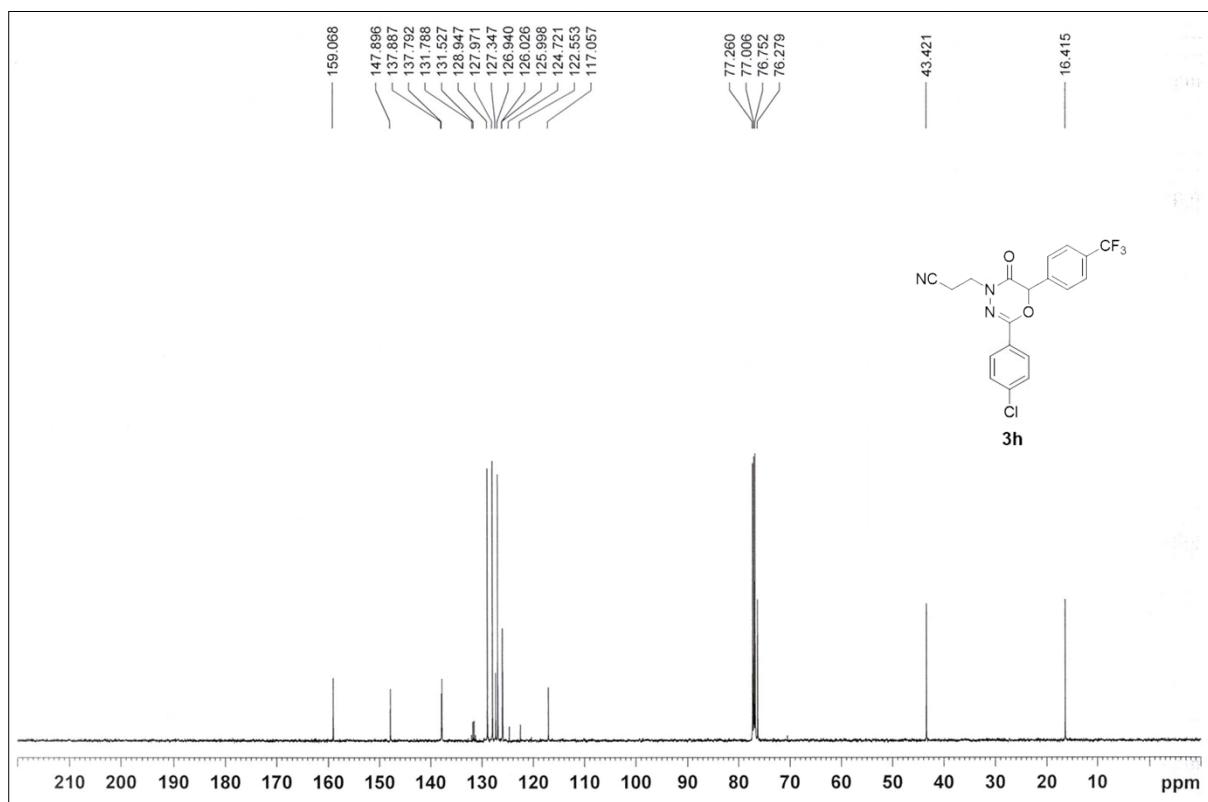
¹³C-NMR of compound **3g** (150 MHz, CDCl₃)



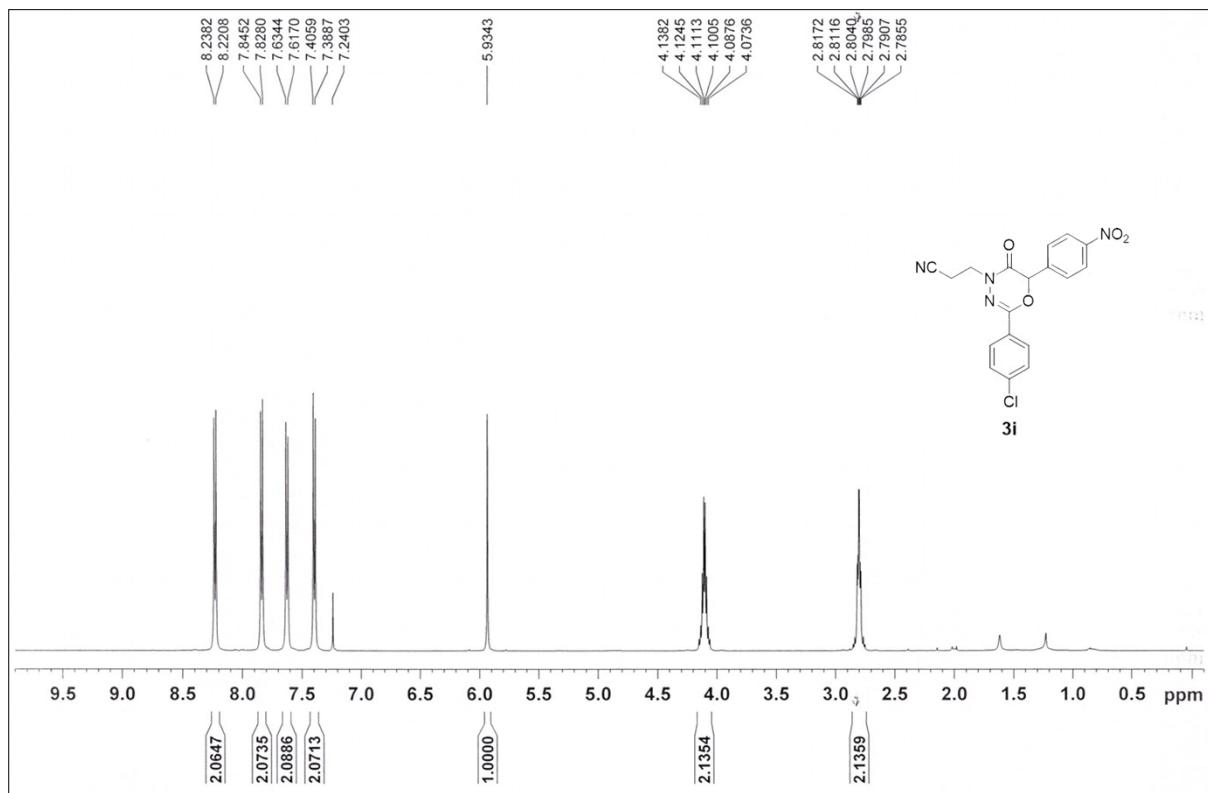
¹H-NMR of compound **3h** (500 MHz, CDCl₃)



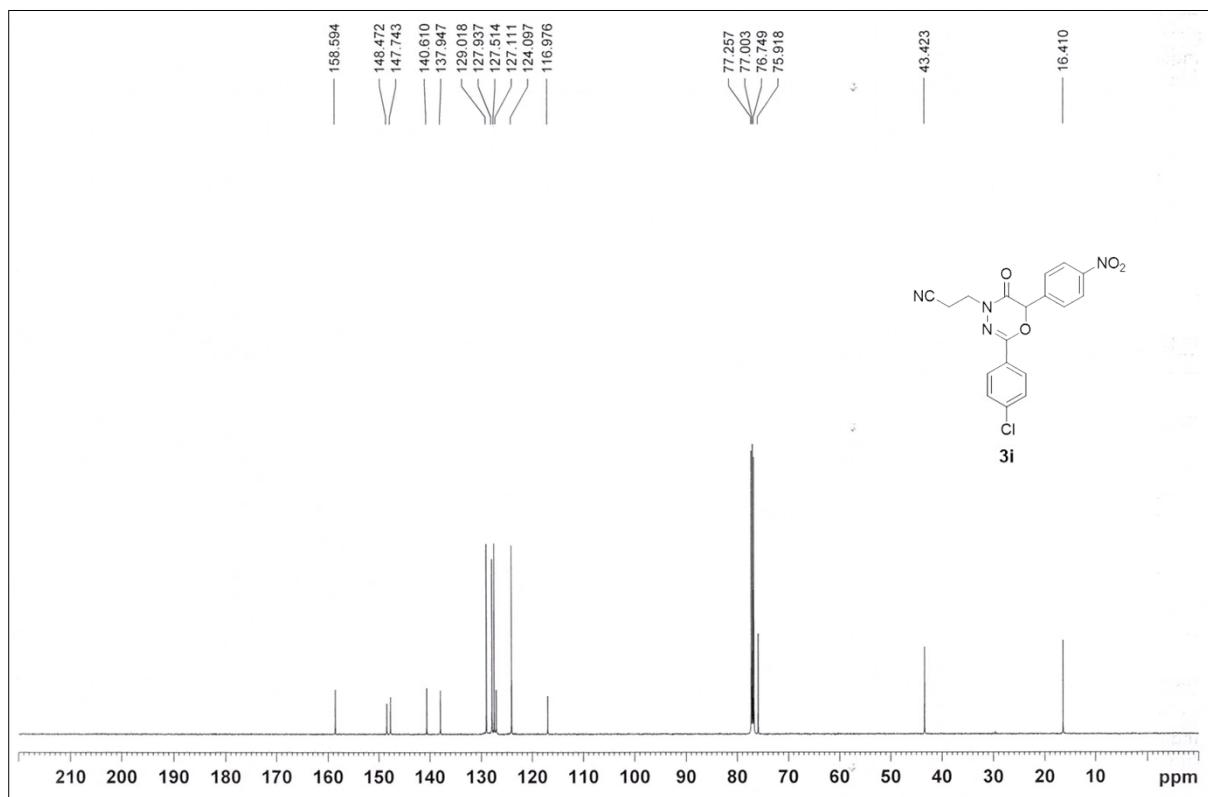
¹³C-NMR of compound **3h** (125 MHz, CDCl₃)



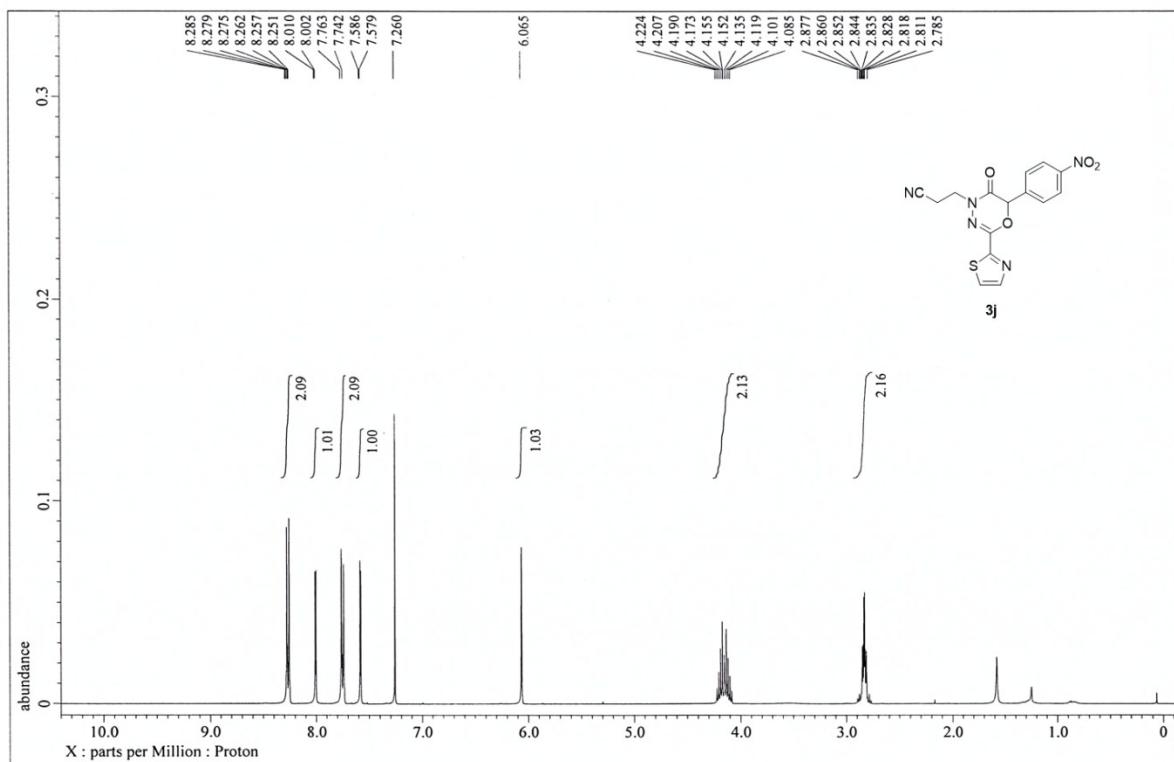
¹H-NMR of compound **3i** (500 MHz, CDCl₃)



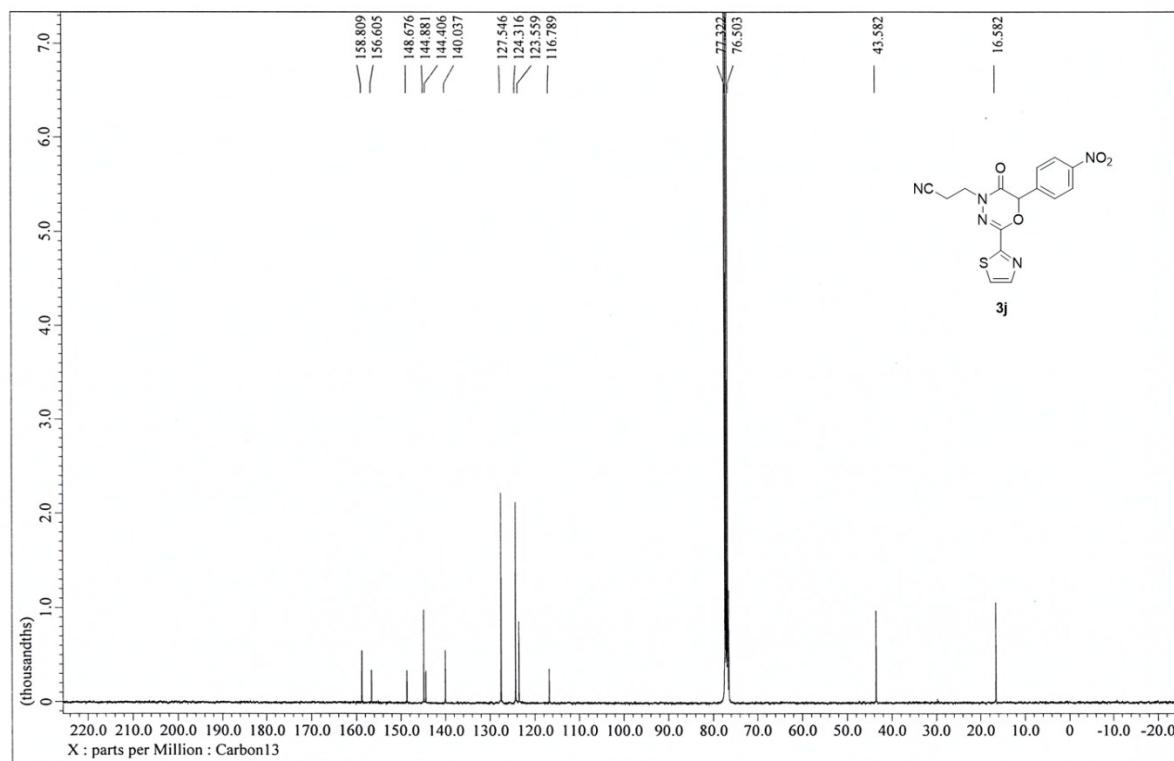
¹³C-NMR of compound **3i** (125 MHz, CDCl₃)



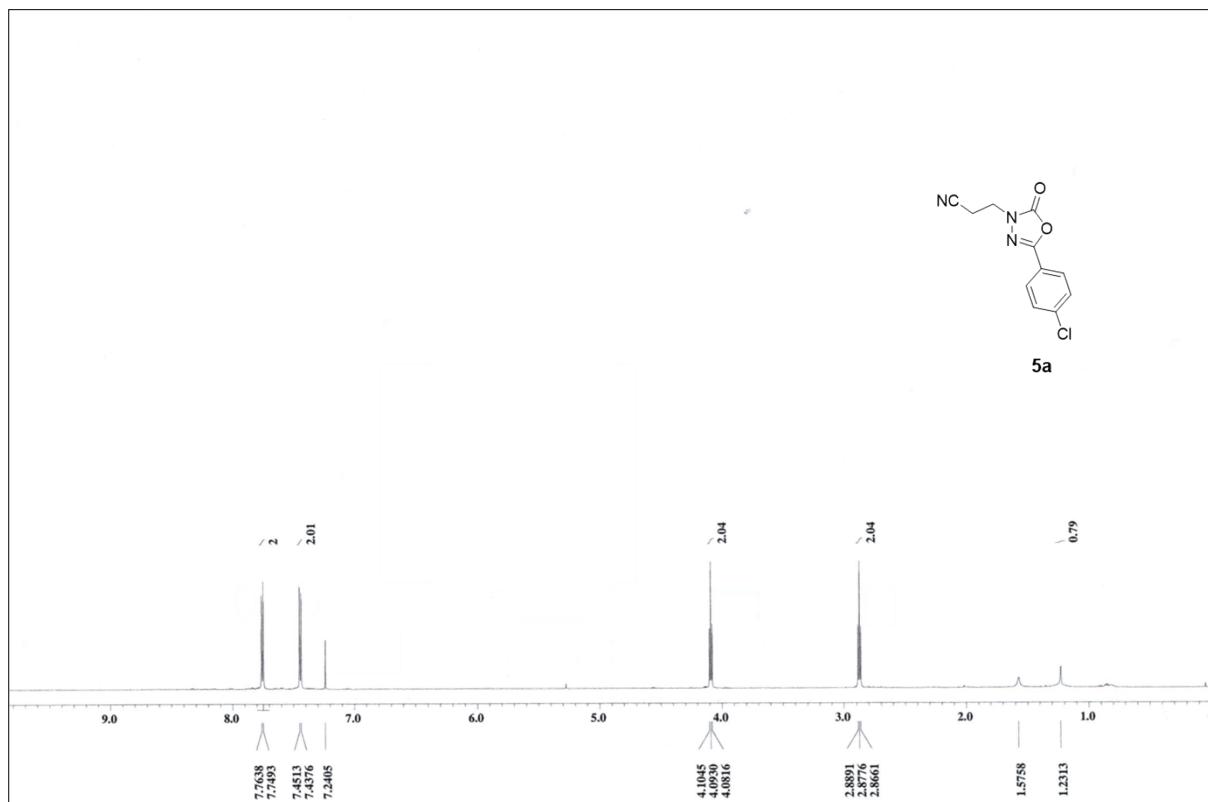
¹H-NMR of compound **3j** (400 MHz, CDCl₃)



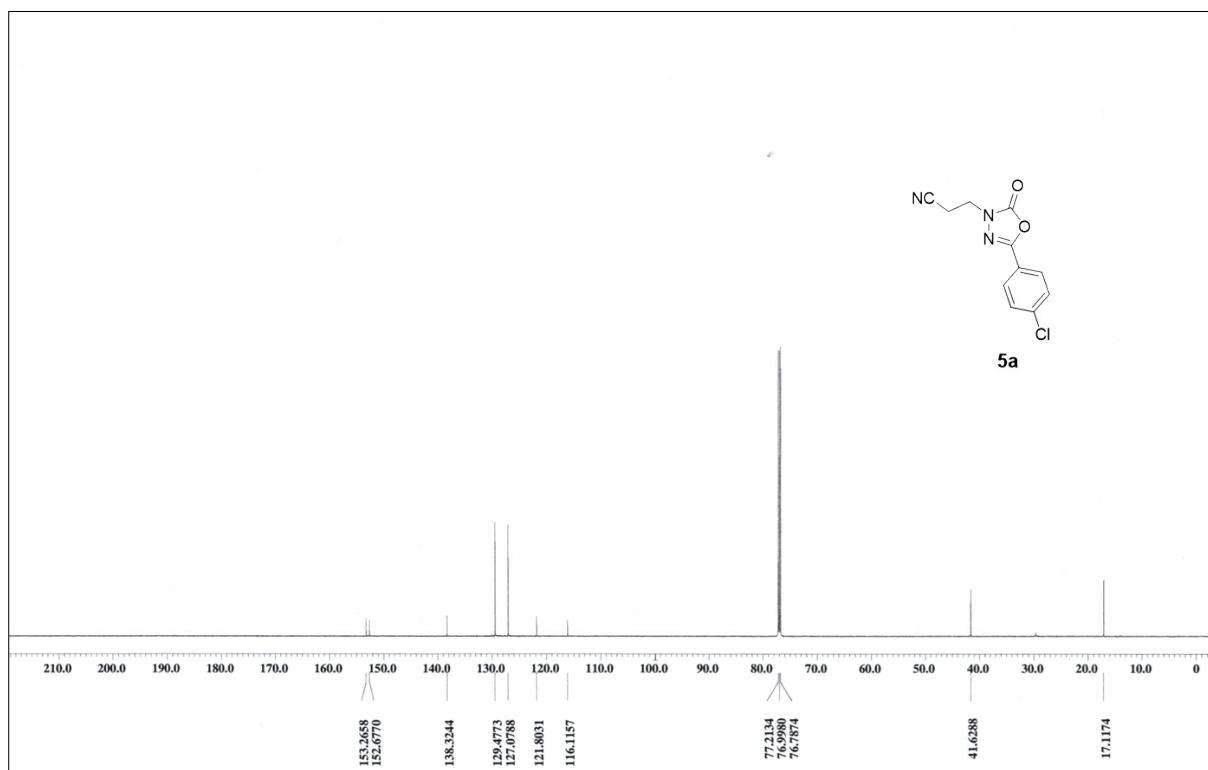
¹³C-NMR of compound **3j** (100 MHz, CDCl₃)



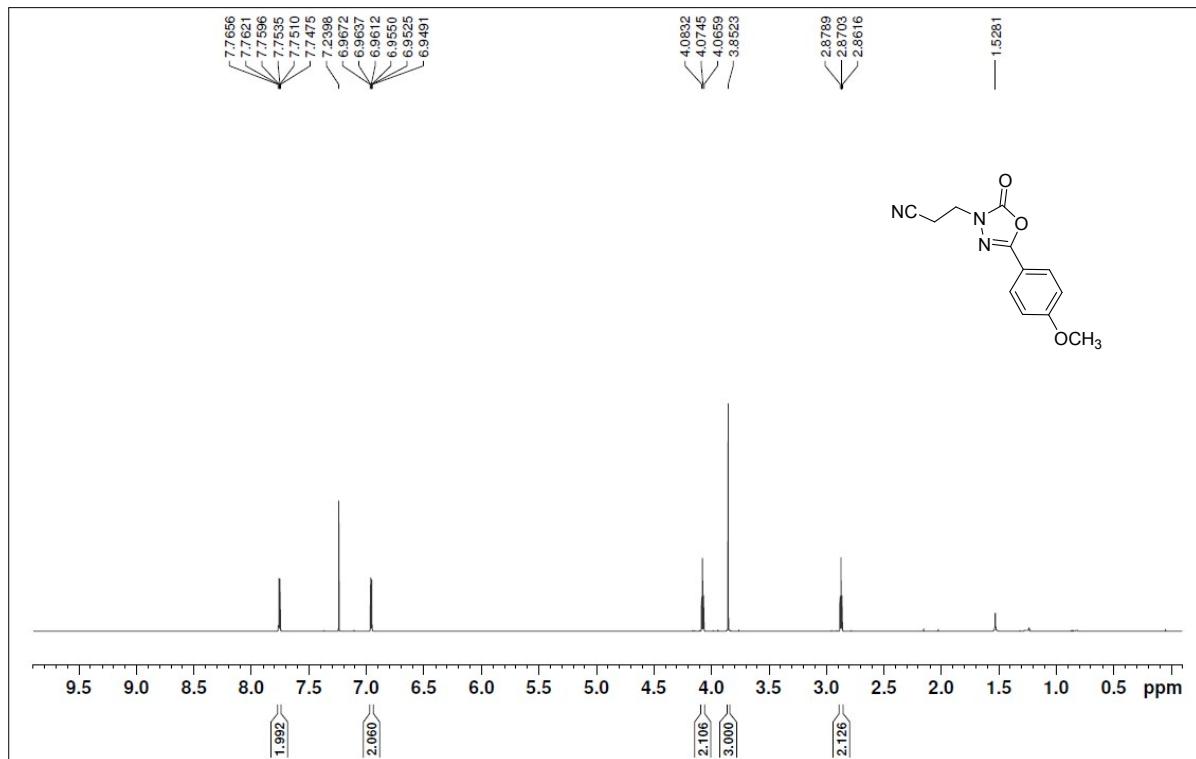
¹H-NMR of compound **5a** (600 MHz, CDCl₃)



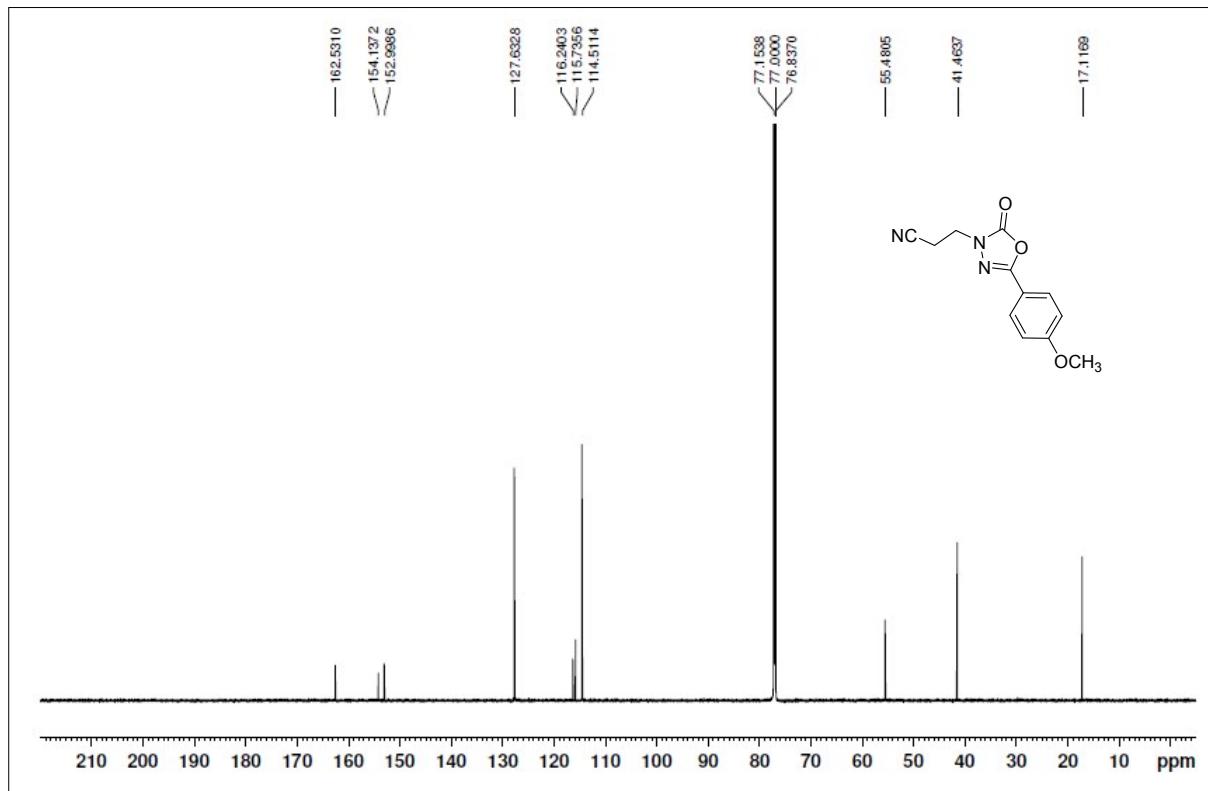
¹³C-NMR of compound **5a** (150 MHz, CDCl₃)



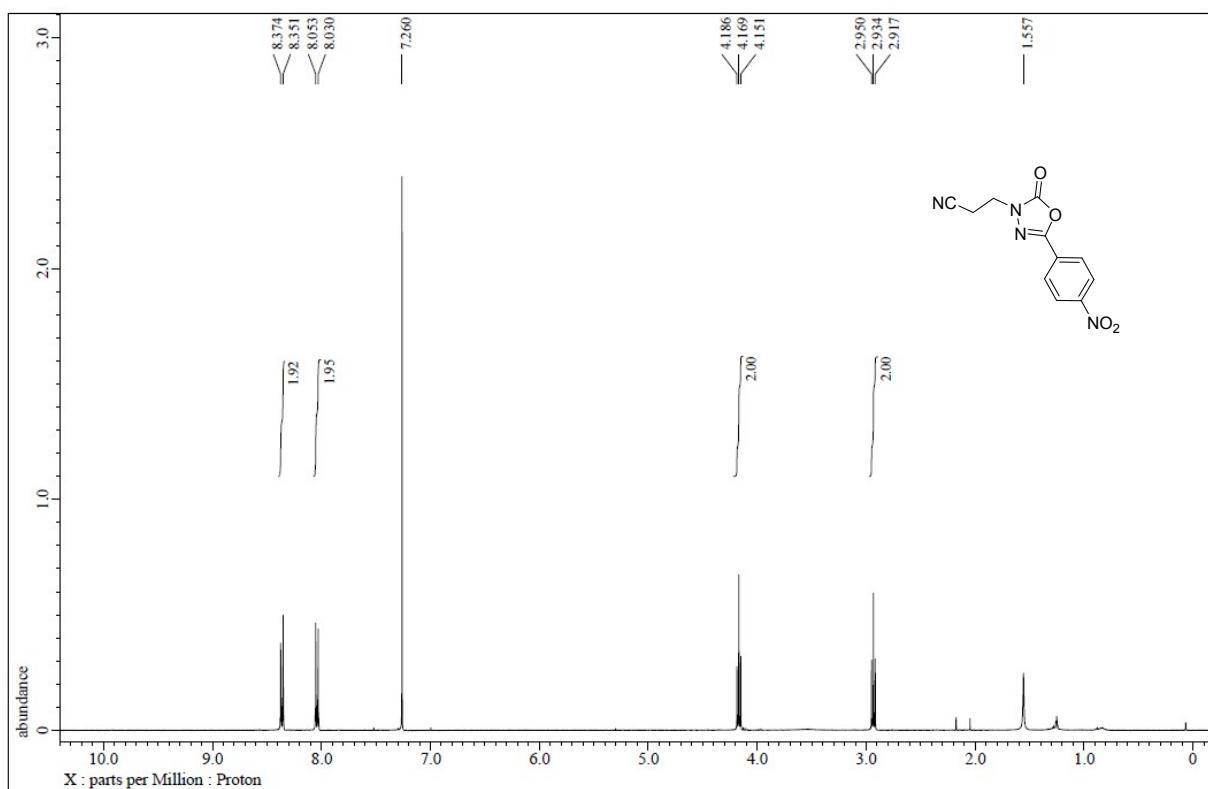
¹H-NMR of compound **5b** (800 MHz, CDCl₃)



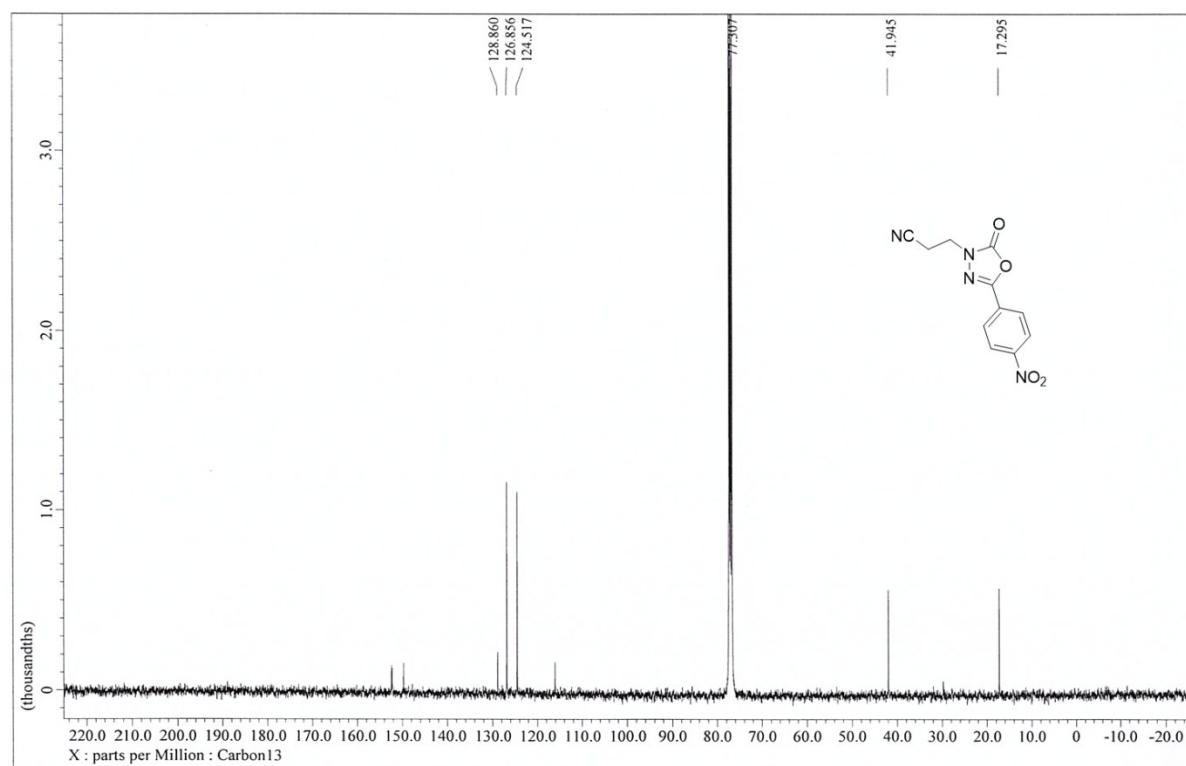
¹³C-NMR of compound **5b** (200 MHz, CDCl₃)



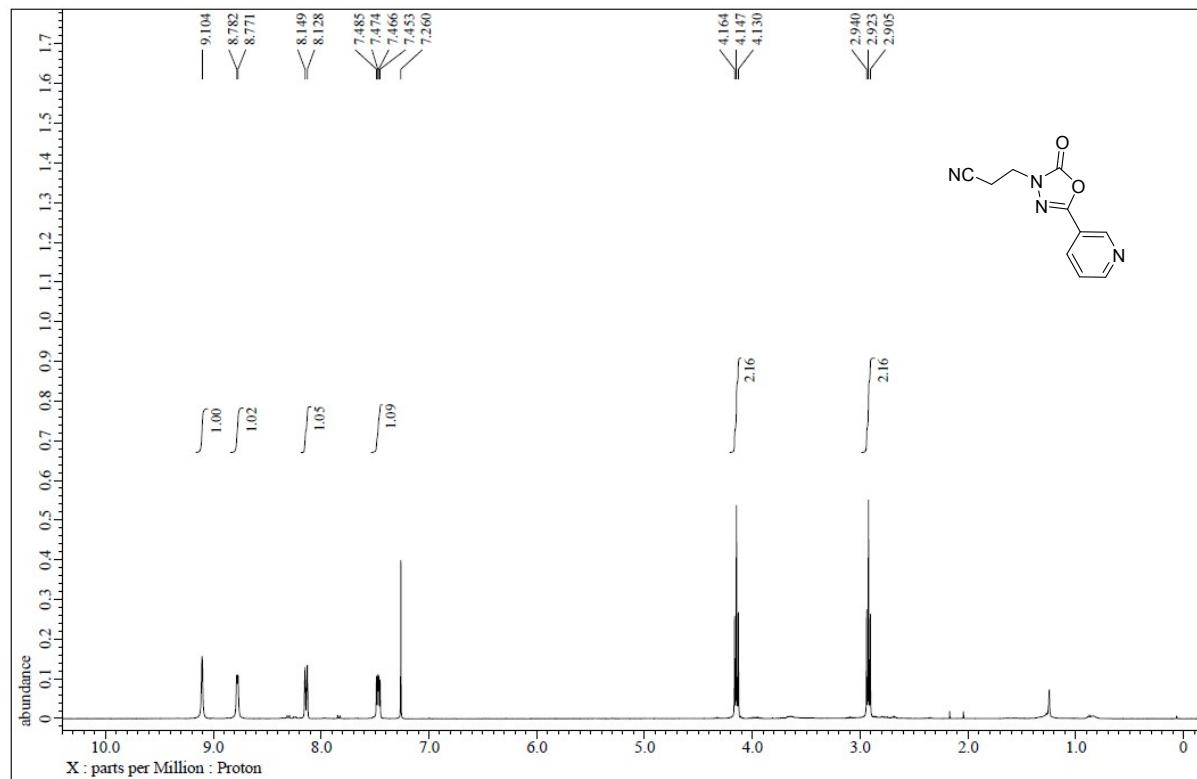
¹H-NMR of compound **5c** (400 MHz, CDCl₃)



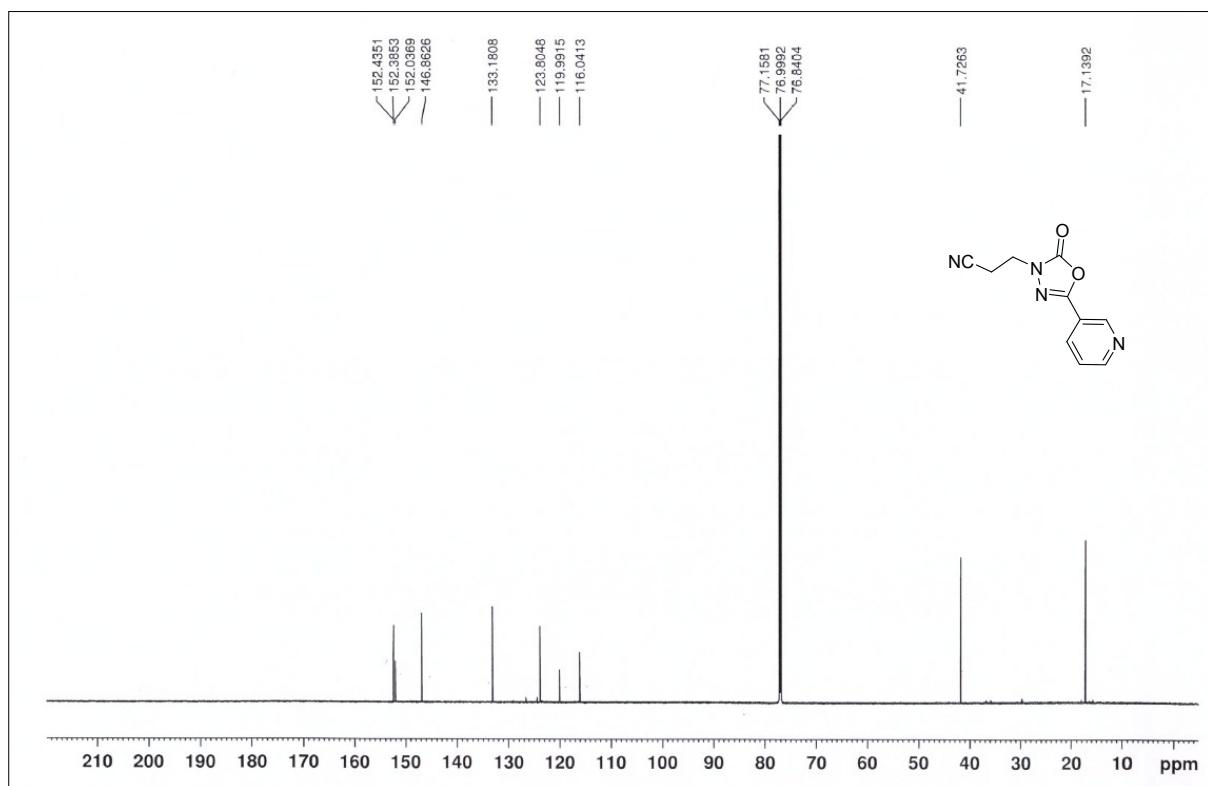
¹³C-NMR of compound **5c** (100 MHz, CDCl₃)



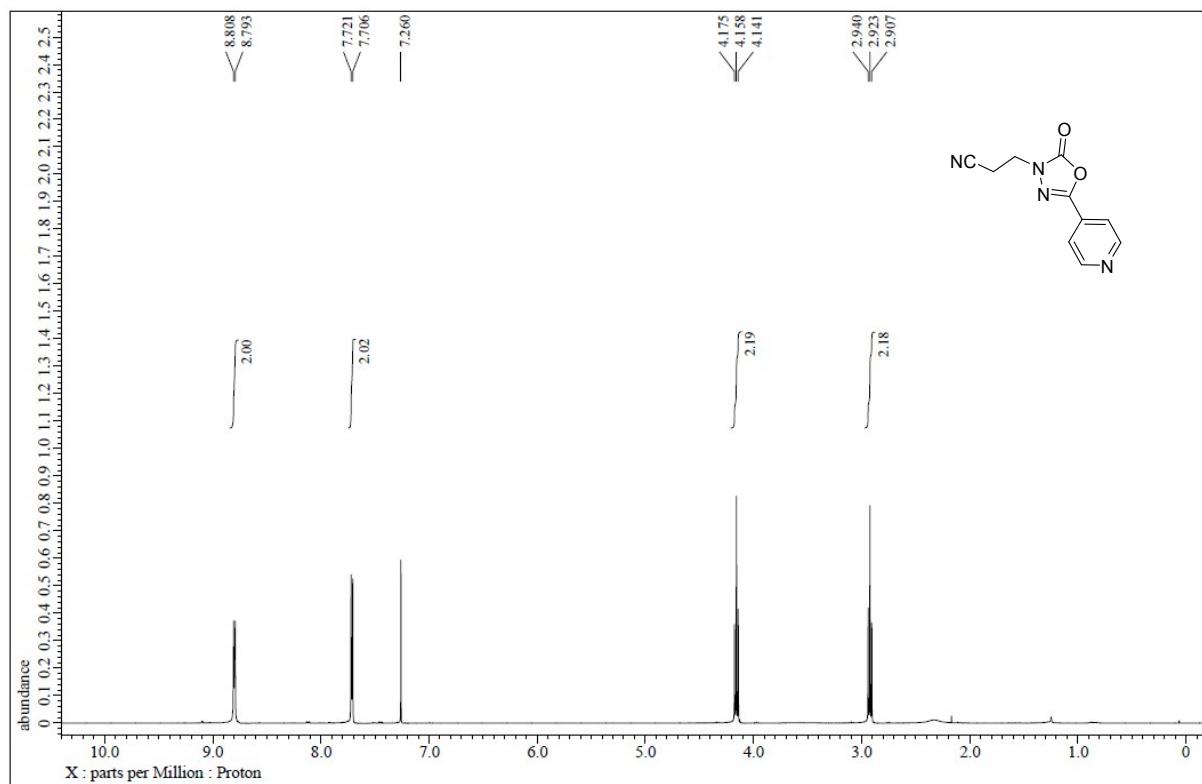
¹H-NMR of compound **5d** (400 MHz, CDCl₃)



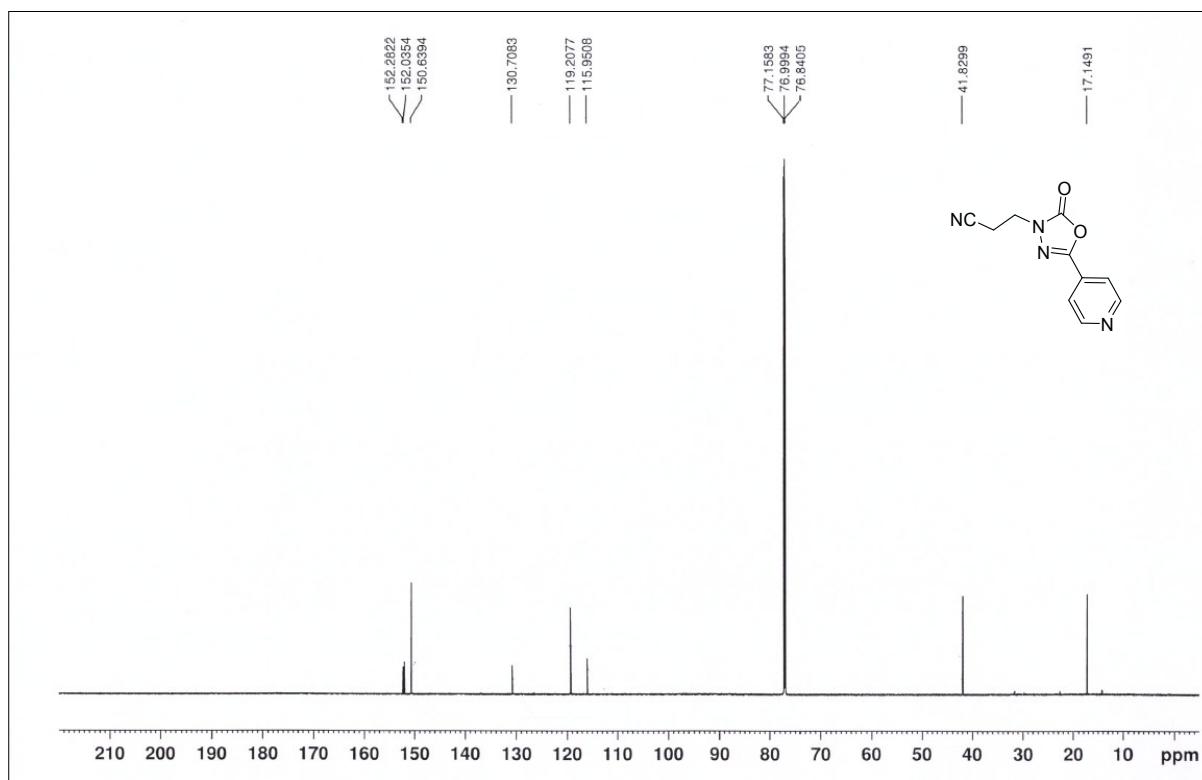
¹³C-NMR of compound **5d** (200 MHz, CDCl₃)



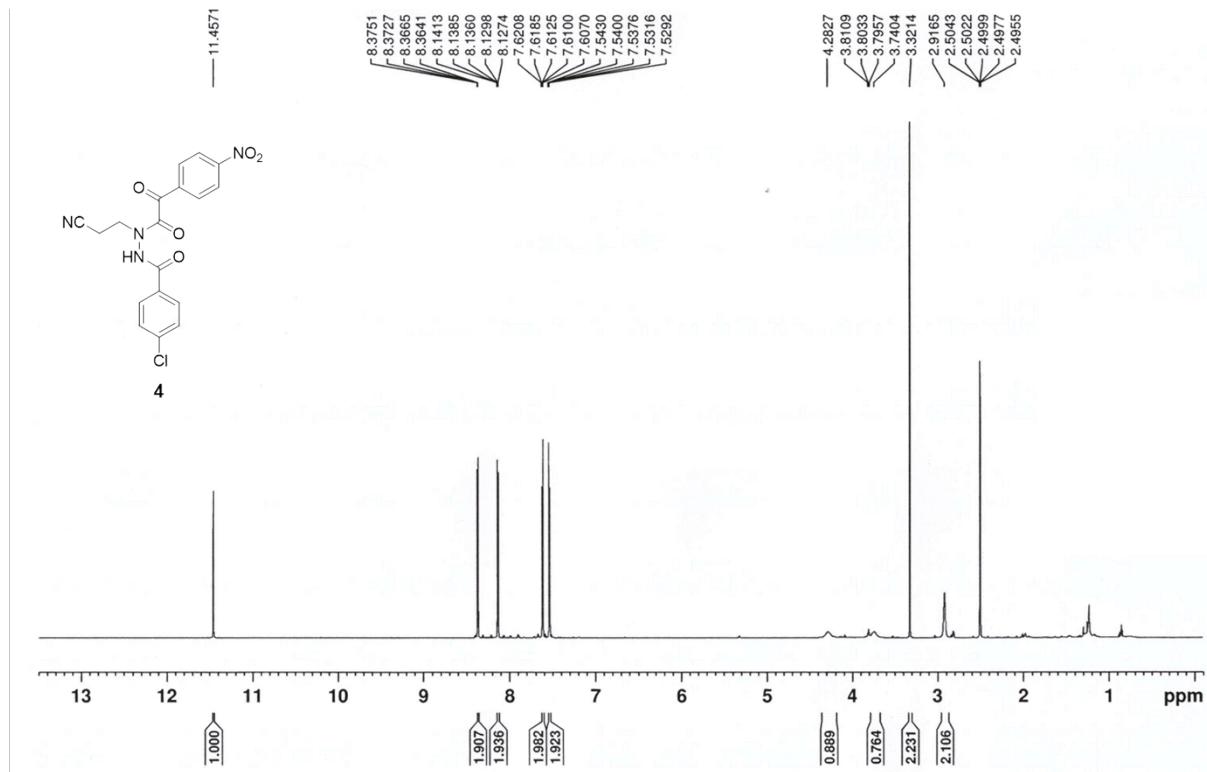
¹H-NMR of compound **5e** (400 MHz, CDCl₃)



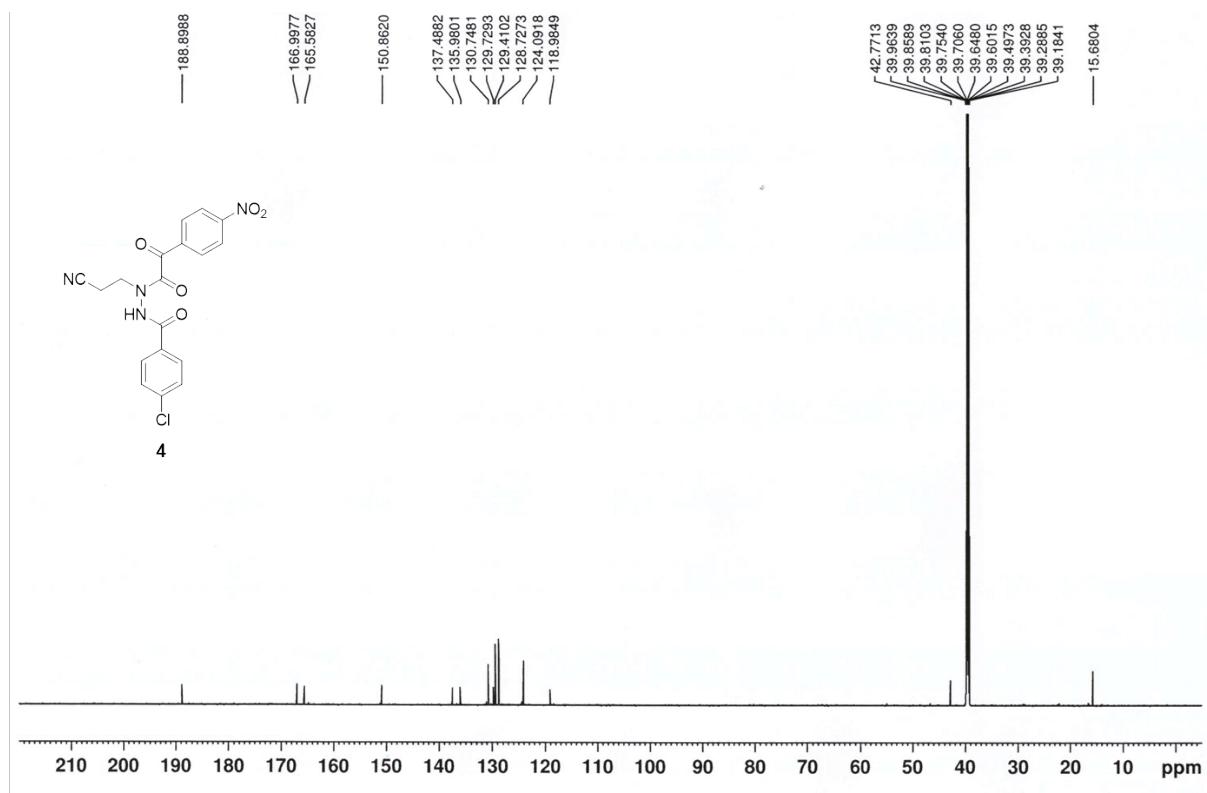
¹³C-NMR of compound **5e** (200 MHz, CDCl₃)



¹H-NMR of compound 4 (800 MHz, DMSO-*d*₆)



¹³C-NMR of compound 4 (200 MHz, DMSO-*d*₆)



II. Supporting Data

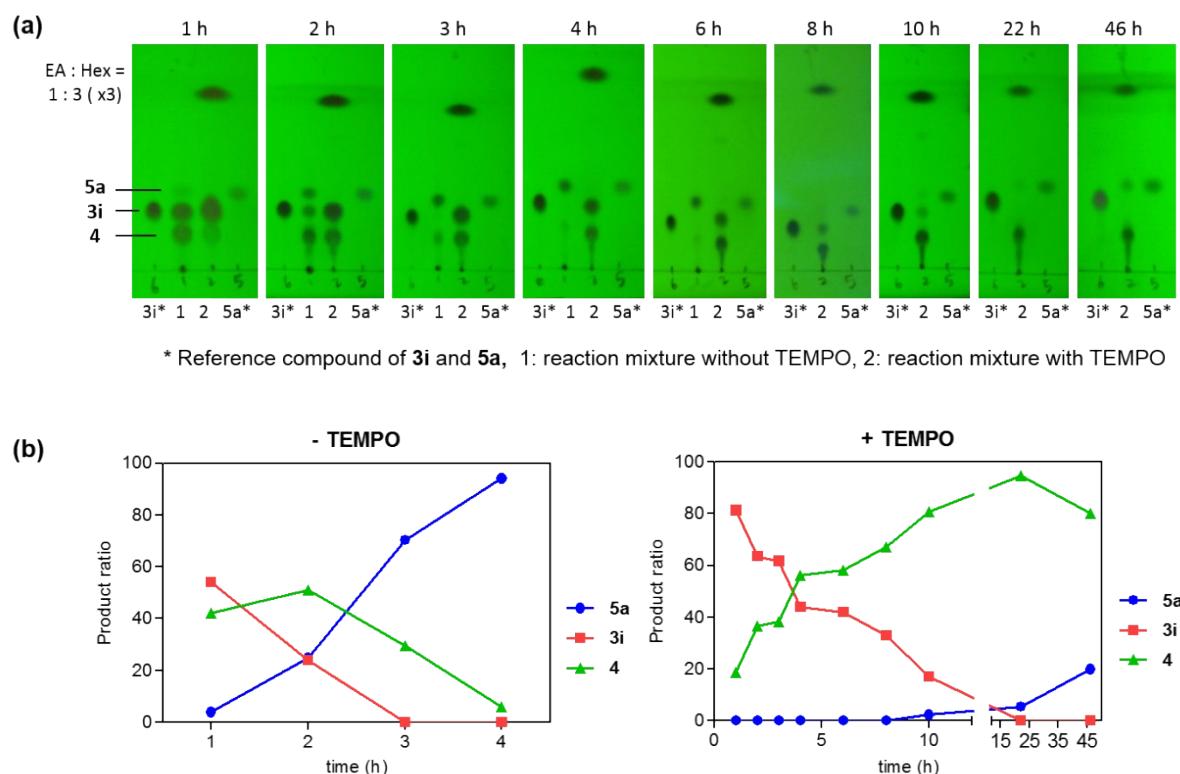


Figure S1. Quantitative TLC analyses demonstrating a reaction progress (from **3i** to **5a**) suppressed by TEMPO (10.0 equiv). **(a)** TLC analysis of the reaction mixture at different time intervals **(b)** Comparison of product ratio in the absence or presence of TEMPO.

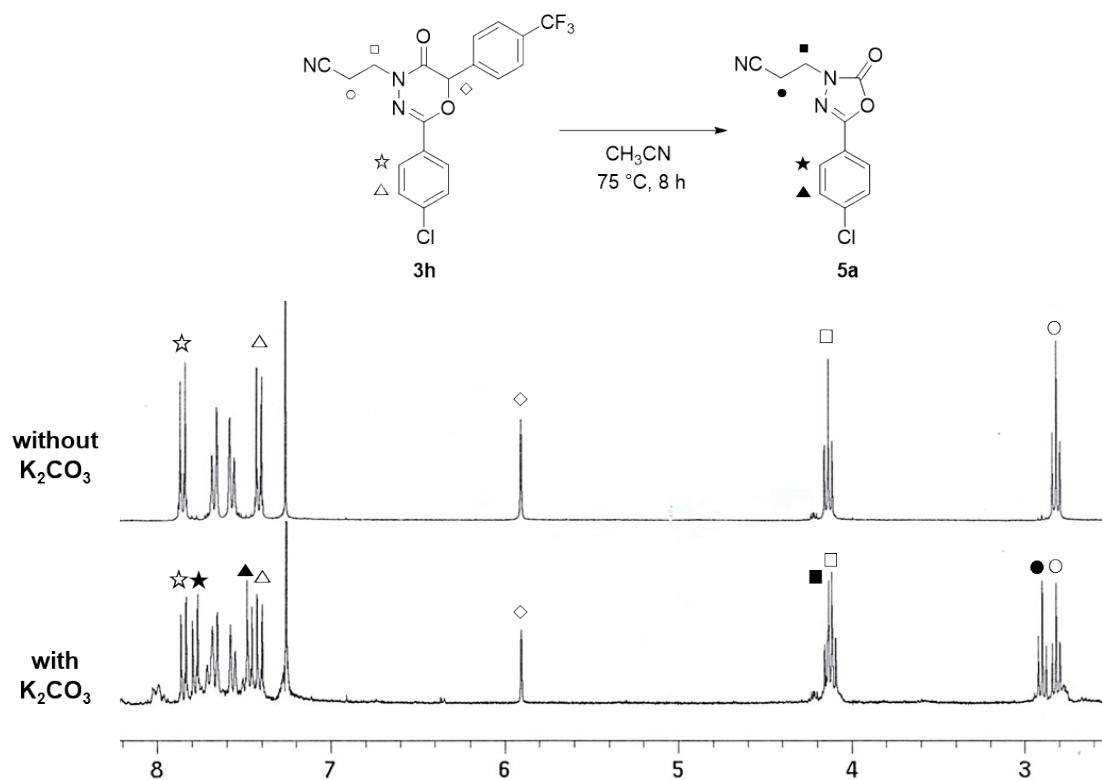


Figure S2. ^1H -NMR analysis of the reaction mixture (300 MHz, CDCl_3) in the presence or absence of K_2CO_3 (Table 2, entry 9-10).

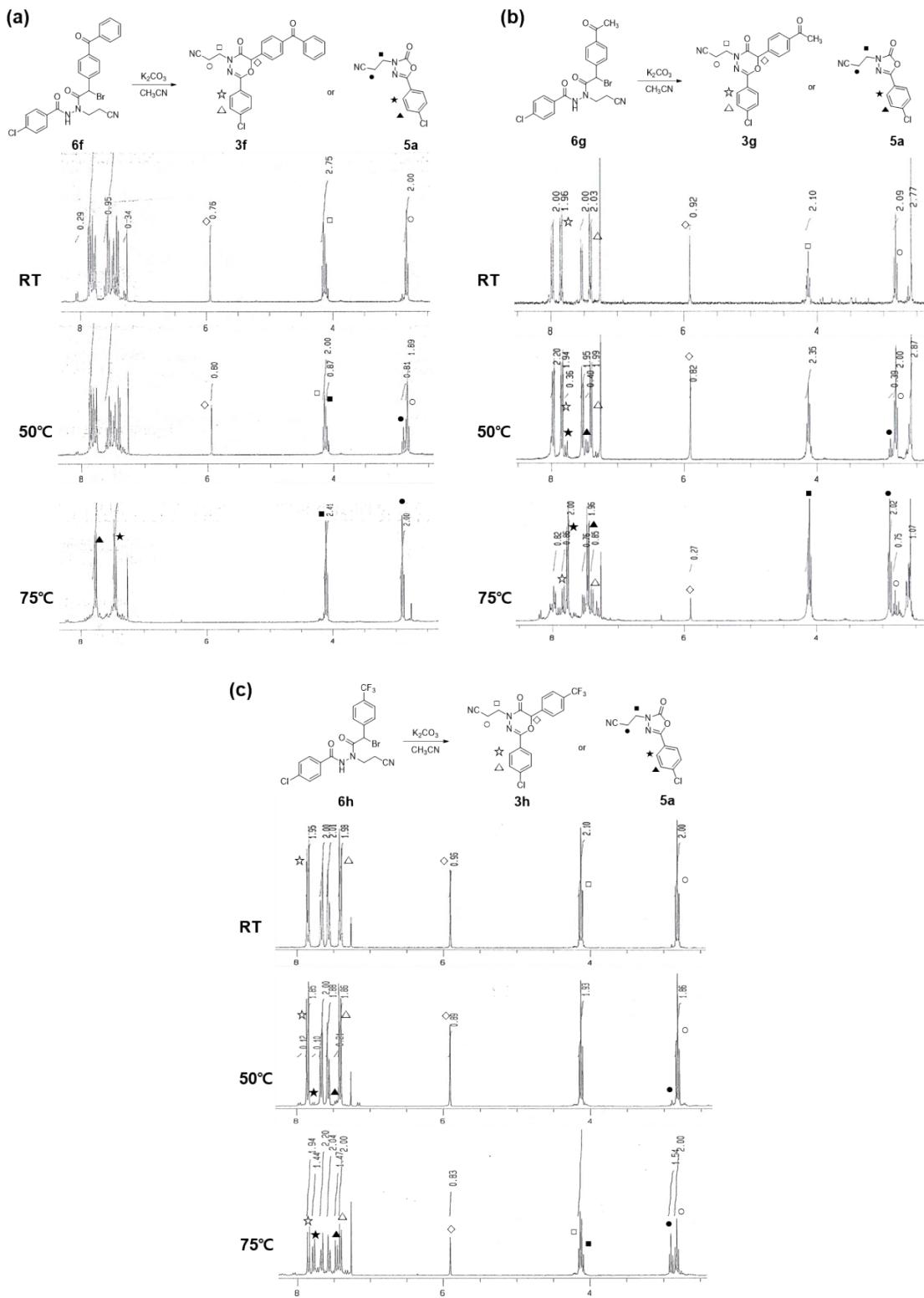


Figure S3. $^1\text{H-NMR}$ analysis of the reaction mixture (300 MHz, CDCl_3) of the cyclization products from **(a) 6f** (Table 3, entry 16-18) **(b) 6g** (Table 3, entry 19-21) **(c) 6h** (Table 3, entry 22-24) at room temperature, 50 °C, and 75 °C, respectively.

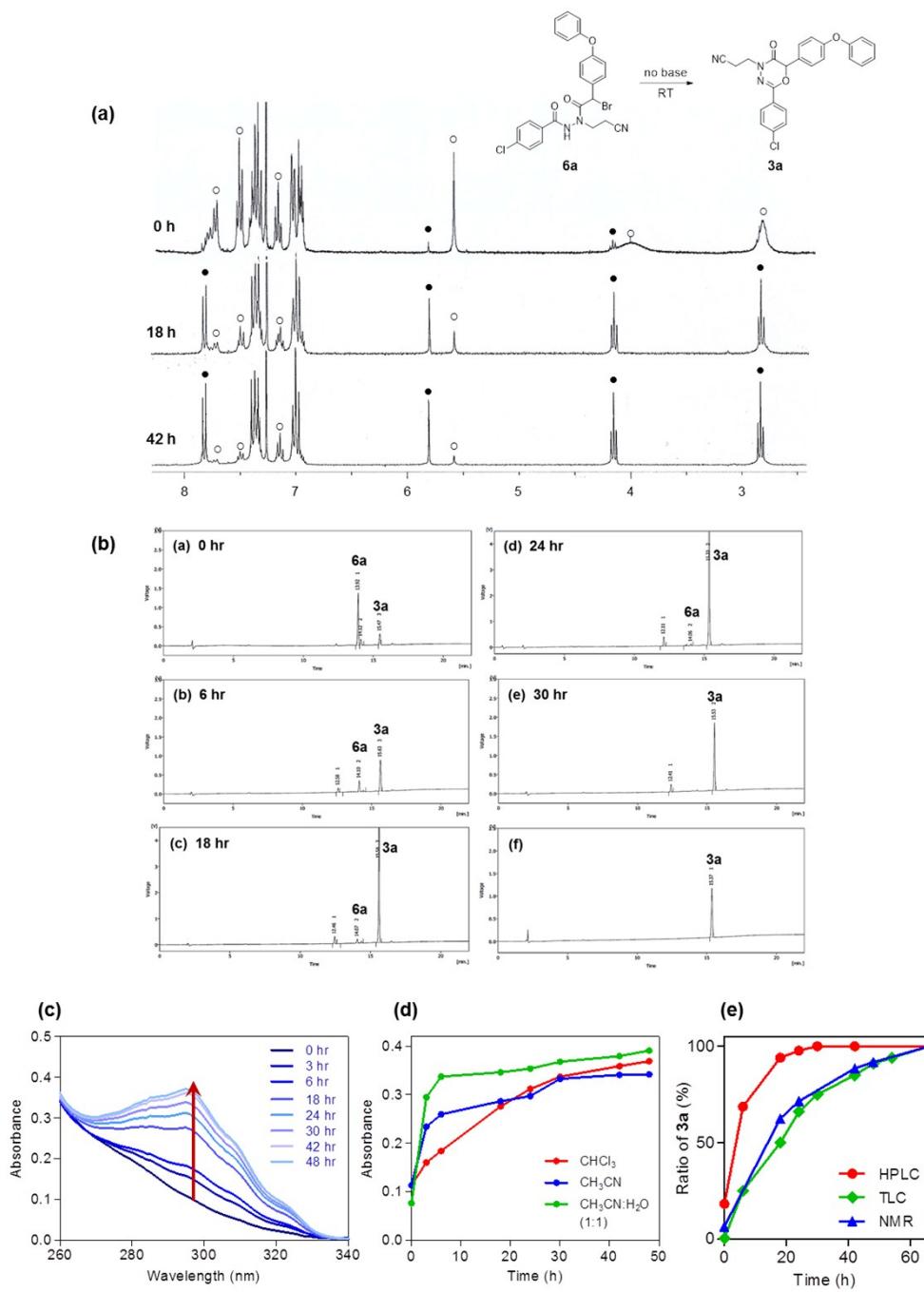


Figure S4. Progress of the spontaneous cyclization reaction of **6a** (○) to **3a** (●) without K₂CO₃ by (a) ¹H-NMR spectra (300 MHz, CDCl₃) and (b) HPLC analysis of the reaction mixture at different time intervals (f: compound **3a** as a reference). (c) Time-dependent changes of UV-Vis absorption spectra, demonstrating the transformation of **6a** to **3a** in CHCl₃. (d) Time-dependent changes of Abs. at 294 nm in various solvents. (e) Comparison of kinetic profiles of the formation of **3a** monitored by HPLC, TLC and ¹H-NMR (red, green and blue), respectively.

III. Single crystal x-ray crystallographic data

Single Crystal X-ray Diffraction Studies

Single crystals of compound **3h** and **5a** with the dimension of $0.263 \times 0.094 \times 0.021$ mm³ and $0.157 \times 0.134 \times 0.069$ mm³, respectively, were obtained by the vapor diffusion method using dichloromethane / hexane solutions. The suitable crystals were introduced into Paraton-N oil and carefully mounted on the top of a nylon loop on SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystal was kept at 99.9 K for compound **3h** and 295.6 K for compound **5a** during data collection performed on SuperNova dual source diffractometer operating with Cu-K α radiation ($\lambda = 1.542$ mm⁻¹). The structure was solved by direct methods with the ShelXT^[1] structure solution program using Olex2^[2] and refined by least squares minimization method using the ShelXL^[3] incorporated in the refinement package. Details for data collection and structure refinement of compound **3h** and **5a** are summarized in Table S1-S12. Supplementary crystallographic data for this paper can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC-1538325 and CCDC-1538326) via www.ccdc.cam.ac.uk/data_request/cif.

Crystal structure determination of 3h

Crystal Data for C₁₉H₁₃ClF₃N₃O₂ ($M = 407.77$ g/mol): monoclinic, space group P2₁/n (no. 14), $a = 5.77529(12)$ Å, $b = 22.1018(5)$ Å, $c = 14.0999(3)$ Å, $\beta = 101.1816(19)^\circ$, $V = 1765.61(6)$ Å³, $Z = 4$, $T = 99.9(3)$ K, $\mu(\text{CuK}\alpha) = 2.396$ mm⁻¹, $D_{\text{calc}} = 1.534$ g/cm³, 23127 reflections measured ($7.54^\circ \leq 2\Theta \leq 153.392^\circ$), 3602 unique ($R_{\text{int}} = 0.0444$, $R_{\text{sigma}} = 0.0332$) which were used in all calculations. The final R_1 was 0.0605 ($I > 2\sigma(I)$) and wR_2 was 0.1110 (all data).

Crystal structure determination of 5a

Crystal Data for C₁₁H₈ClN₃O₂ ($M = 249.65$ g/mol): triclinic, space group P-1 (no. 2), $a = 5.7810(2)$ Å, $b = 8.5176(3)$ Å, $c = 11.7466(4)$ Å, $\alpha = 102.453(3)^\circ$, $\beta = 90.500(2)^\circ$, $\gamma = 98.113(2)^\circ$, $V = 558.69(3)$ Å³, $Z = 2$, $T = 295.6(2)$ K, $\mu(\text{CuK}\alpha) = 2.993$ mm⁻¹, $D_{\text{calc}} = 1.484$ g/cm³, 10790 reflections measured

($7.714^\circ \leq 2\Theta \leq 152.808^\circ$), 2339 unique ($R_{\text{int}} = 0.0198$, $R_{\text{sigma}} = 0.0140$) which were used in all calculations. The final R_1 was 0.0345 ($I > 2\sigma(I)$) and wR_2 was 0.0989 (all data).

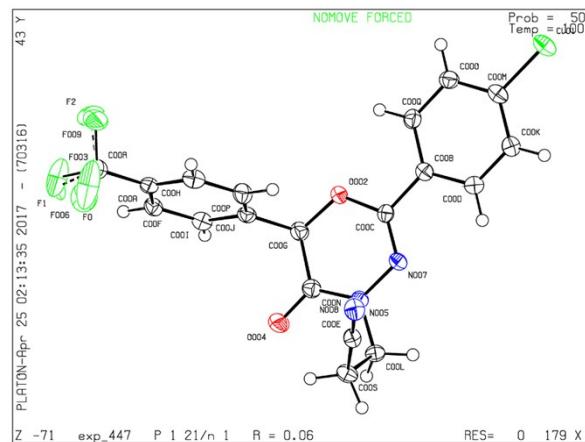


Figure S5. Molecular structure of compound **3h** in the crystal; thermal ellipsoids are drawn at 50 % probability level.

Table S1. Crystal data and structure refinement for **3h**

Identification code	exp_447
Empirical formula	C ₁₉ H ₁₃ ClF ₃ N ₃ O ₂
Formula weight	407.77
Temperature/K	99.9(3)
Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	5.77529(12)
b/Å	22.1018(5)
c/Å	14.0999(3)
α/°	90
β/°	101.1816(19)
γ/°	90
Volume/Å ³	1765.61(6)
Z	4
ρ _{calc} g/cm ³	1.534
μ/mm ⁻¹	2.396
F(000)	832.0
Crystal size/mm ³	0.263 × 0.094 × 0.021
Radiation	CuKα ($\lambda = 1.54184$)
2Θ range for data collection/°	7.54 to 153.392
Index ranges	-7 ≤ h ≤ 7, -26 ≤ k ≤ 27, -17 ≤ l ≤ 12
Reflections collected	23127

Independent reflections	3602 [R _{int} = 0.0444, R _{sigma} = 0.0332]
Data/restraints/parameters	3602/0/281
Goodness-of-fit on F ²	1.118
Final R indexes [I>=2σ (I)]	R ₁ = 0.0605, wR ₂ = 0.1087
Final R indexes [all data]	R ₁ = 0.0647, wR ₂ = 0.1110
Largest diff. peak/hole / e Å ⁻³	0.36/-0.40

Table S2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for compound **3h**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	x	y	z	U(eq)
Cl01	12027.8(9)	9404.5(3)	6634.9(4)	29.70(15)
O002	2658(3)	7702.4(7)	4905.0(12)	30.3(4)
F003	677(19)	4559(3)	3589(7)	47.1(18)
O004	-2994(3)	7502.3(7)	3318.1(12)	31.9(4)
N005	-507(3)	8300.2(8)	3537.8(12)	19.5(4)
F006	2090(20)	4912(6)	2465(7)	53(2)
N007	1585(3)	8581.7(8)	3991.3(12)	20.3(4)
N008	2445(3)	8265.4(9)	1505.3(14)	27.5(4)
F009	4359(15)	4762(5)	3784(14)	57(3)
C00A	1728(4)	5586.9(10)	3717.9(15)	21.1(4)
C00B	5229(4)	8548.4(9)	5114.1(14)	19.4(4)
C00C	2983(4)	8275.7(9)	4621.8(14)	19.0(4)
C00D	5806(4)	9136.6(10)	4883.7(15)	20.9(4)
C00E	559(4)	8347.2(9)	1619.6(15)	21.5(4)
C00F	-183(4)	5715.3(10)	4146.6(15)	22.3(4)
C00G	431(4)	7401(1)	4562.6(16)	24.0(5)
C00H	3238(4)	6049.5(11)	3558.3(16)	25.6(5)
C00I	-572(4)	6299.7(10)	4419.4(15)	22.6(4)
C00J	925(4)	6763.4(10)	4260.5(15)	21.6(4)
C00K	7889(4)	9400.6(10)	5354.9(15)	22.5(4)
C00L	-1967(4)	8659.8(10)	2785.5(15)	21.3(4)
C00M	9411(4)	9070.2(10)	6047.7(15)	22.3(4)
C00N	-1167(4)	7736.7(10)	3745.0(16)	23.4(4)
C00O	8881(4)	8487.4(10)	6283.4(16)	24.6(5)
C00P	2832(4)	6637.1(10)	3826.1(16)	26.3(5)
C00Q	6768(4)	8228.4(10)	5819.6(16)	24.4(4)
C00R	2202(4)	4958.1(11)	3424.0(17)	29.0(5)
C00S	-1853(4)	8424.2(11)	1773.8(15)	24.1(5)
F0	2680(50)	4914(7)	2560(14)	69(5)
F1	350(20)	4592(5)	3484(8)	61(3)
F2	3880(50)	4701(8)	4125(17)	69(5)

Table S3. Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for compound **3h**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^*{}^2U_{11} + 2hka^*b^*U_{12} + \dots]$.

Atom	U11	U22	U33	U23	U13	U12
Cl01	21.8(3)	41.4(3)	25.6(3)	-4.4(2)	3.7(2)	-8.1(2)
O002	26.8(8)	20.5(8)	37.6(9)	3.6(7)	-8.9(7)	-5.4(6)
F003	67(3)	25(2)	67(3)	-1(2)	58(3)	-2(2)
O004	22.6(8)	30.9(9)	38.9(10)	5.5(7)	-1.9(7)	-6.8(7)
N005	17.0(8)	20.9(9)	20.4(9)	-0.1(7)	3.6(7)	-1.1(7)
F006	77(4)	47(3)	36(3)	-16(2)	11(4)	8(3)
N007	17.5(8)	23.4(9)	19.7(9)	-1.0(7)	3.3(7)	-2.5(7)
N008	25.6(10)	29(1)	29.8(10)	-2.0(8)	10.2(8)	-1.6(8)
F009	33(2)	42(3)	83(6)	-27(4)	-21(3)	20.2(18)
C00A	22.9(10)	23.6(10)	15.4(9)	0.0(8)	-0.2(8)	0.3(8)
C00B	19.5(10)	22.3(10)	17.4(10)	-3.3(8)	6.2(8)	0.5(8)
C00C	20.2(10)	18.1(10)	19.7(10)	-2.0(8)	6.5(8)	0.9(8)
C00D	19.9(10)	25.1(11)	19.1(10)	1.4(8)	6.7(8)	1.2(8)
C00E	24.0(11)	21.7(10)	19.3(10)	-0.3(8)	5.5(8)	-2.9(8)
C00F	20.8(10)	25.1(11)	20.9(10)	1.1(8)	4.0(8)	-4.3(8)
C00G	24.1(11)	23.6(11)	23.7(11)	1.1(8)	2.9(9)	-3.4(8)
C00H	20.8(10)	35.1(12)	22.1(11)	1.8(9)	7.0(8)	0.3(9)
C00I	20.4(10)	28.3(11)	19.6(10)	-0.7(8)	5.1(8)	-0.2(8)
C00J	21.3(10)	24.7(11)	17.2(10)	1.3(8)	-0.1(8)	-0.2(8)
C00K	22.4(10)	24.5(11)	22.2(10)	-0.1(8)	8.5(8)	-2.9(8)
C00L	18.2(10)	24.7(11)	21.3(10)	1.7(8)	4.7(8)	2.7(8)
C00M	18.8(10)	31.1(11)	18(1)	-5.6(8)	5.5(8)	-2.1(8)
C00N	20.9(10)	24.2(11)	25.3(11)	-0.3(9)	5.3(9)	-0.5(8)
C00O	24.0(11)	26.5(11)	22.1(11)	-1.1(9)	1.6(9)	2.6(9)
C00P	24.2(11)	26.2(11)	28.9(12)	4.9(9)	6.1(9)	-7.2(9)
C00Q	27.5(11)	20.2(10)	25.0(11)	-1.6(8)	4.3(9)	0.2(9)
C00R	27.7(11)	29.2(12)	28.8(12)	-2.6(9)	2.0(9)	2.3(9)
C00S	18.8(10)	32.0(12)	21.8(11)	-1.4(9)	4.5(8)	-1.1(9)
F0	132(11)	32(4)	69(8)	-9(5)	89(8)	-13(6)
F1	43(3)	26(4)	100(7)	-18(3)	-21(6)	-12(3)
F2	76(9)	43(4)	69(8)	-24(5)	-35(6)	35(5)

Table S4. Bond Lengths for compound **3h**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl01	C00M	1.741(2)	C00B	C00Q	1.392(3)
O002	C00C	1.353(2)	C00D	C00K	1.385(3)
O002	C00G	1.446(2)	C00E	C00S	1.461(3)
F003	C00R	1.299(6)	C00F	C00I	1.378(3)
O004	C00N	1.224(3)	C00G	C00J	1.515(3)
N005	N007	1.399(2)	C00G	C00N	1.523(3)
N005	C00L	1.456(3)	C00H	C00P	1.385(3)
N005	C00N	1.351(3)	C00I	C00J	1.387(3)
F006	C00R	1.346(10)	C00J	C00P	1.389(3)
N007	C00C	1.273(3)	C00K	C00M	1.388(3)
N008	C00E	1.146(3)	C00L	C00S	1.532(3)

F009	C00R	1.323(9)	C00M	C00O	1.379(3)
C00A	C00F	1.387(3)	C00O	C00Q	1.391(3)
C00A	C00H	1.390(3)	C00R	F0	1.303(13)
C00A	C00R	1.491(3)	C00R	F1	1.359(10)
C00B	C00C	1.476(3)	C00R	F2	1.366(14)
C00B	C00D	1.396(3)			

Table S5. Bond Angles for compound **3h**.

Atom	Atom	Atom	Angle/ ^o	Atom	Atom	Atom	Angle/ ^o
C00C	O002	C00G	119.90(16)	C00D	C00K	C00M	119.2(2)
N007	N005	C00L	114.65(16)	N005	C00L	C00S	111.68(17)
C00N	N005	N007	124.49(17)	C00K	C00M	Cl01	118.96(17)
C00N	N005	C00L	120.86(17)	C00O	C00M	Cl01	119.66(17)
C00C	N007	N005	117.23(17)	C00O	C00M	C00K	121.4(2)
C00F	C00A	C00H	119.8(2)	O004	C00N	N005	122.4(2)
C00F	C00A	C00R	121.1(2)	O004	C00N	C00G	120.28(19)
C00H	C00A	C00R	119.1(2)	N005	C00N	C00G	117.27(18)
C00D	C00B	C00C	119.90(18)	C00M	C00O	C00Q	119.1(2)
C00Q	C00B	C00C	120.66(19)	C00H	C00P	C00J	120.0(2)
C00Q	C00B	C00D	119.43(19)	C00O	C00Q	C00B	120.5(2)
O002	C00C	C00B	113.79(17)	F003	C00R	F006	103.1(6)
N007	C00C	O002	126.73(19)	F003	C00R	F009	109.3(6)
N007	C00C	C00B	119.48(18)	F003	C00R	C00A	114.5(3)
C00K	C00D	C00B	120.3(2)	F006	C00R	C00A	112.0(6)
N008	C00E	C00S	177.6(2)	F009	C00R	F006	102.5(8)
C00I	C00F	C00A	120.0(2)	F009	C00R	C00A	114.1(5)
O002	C00G	C00J	108.58(17)	F0	C00R	C00A	114.4(7)
O002	C00G	C00N	113.42(17)	F0	C00R	F1	108.9(11)
C00J	C00G	C00N	111.09(18)	F0	C00R	F2	113.4(9)
C00P	C00H	C00A	120.1(2)	F1	C00R	C00A	110.4(5)
C00F	C00I	C00J	120.5(2)	F1	C00R	F2	99.5(12)
C00I	C00J	C00G	118.99(19)	F2	C00R	C00A	109.2(6)
C00I	C00J	C00P	119.7(2)	C00E	C00S	C00L	113.11(18)
C00P	C00J	C00G	121.31(19)				

Table S6. Hydrogen Atom Coordinates ($\text{A} \times 10^4$) and Isotropic Displacement Parameters ($\text{A}^2 \times 10^3$) for compound **3h**.

Atom	x	y	z	U(eq)
H00D	4787	9352	4411	25
H00F	-1202	5407	4250	27
H00G	-398	7372	5105	29
H00H	4522	5964	3272	31
H00I	-1848	6384	4712	27
H00K	8263	9795	5209	27
H00A	-1438	9077	2842	26
H00B	-3590	8650	2875	26

H00O	9922	8271	6746	30
H00P	3836	6947	3715	32
H00Q	6381	7838	5982	29
H00C	-2666	8038	1676	29
H00E	-2677	8705	1296	29

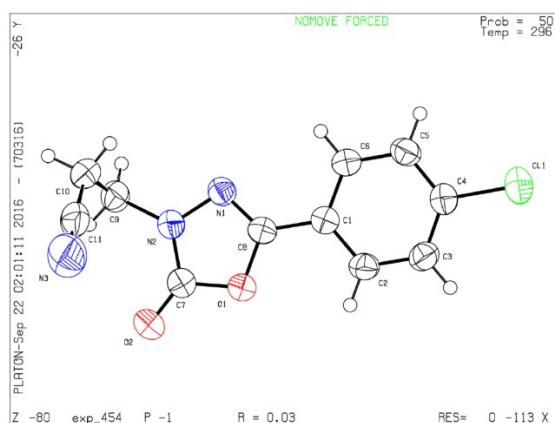


Figure S6. Molecular structure of compound **5a** in the crystal; thermal ellipsoids are drawn at 50 % probability level.

Table S7. Crystal data and structure refinement for **5a**

Identification code	exp_454
Empirical formula	C ₁₁ H ₈ ClN ₃ O ₂
Formula weight	249.65
Temperature/K	295.6(2)
Crystal system	triclinic
Space group	P-1
a/Å	5.7810(2)
b/Å	8.5176(3)
c/Å	11.7466(4)
$\alpha/^\circ$	102.453(3)
$\beta/^\circ$	90.500(2)
$\gamma/^\circ$	98.113(2)
Volume/Å ³	558.69(3)
Z	2
ρ_{calc} /g/cm ³	1.484
μ /mm ⁻¹	2.993
F(000)	256.0
Crystal size/mm ³	0.157 × 0.134 × 0.069
Radiation	CuK α ($\lambda = 1.54184$)
2 Θ range for data collection/°	7.714 to 152.808
Index ranges	-7 ≤ h ≤ 7, -10 ≤ k ≤ 10, -14 ≤ l ≤ 14

Reflections collected	10790
Independent reflections	2339 [$R_{\text{int}} = 0.0198$, $R_{\text{sigma}} = 0.0140$]
Data/restraints/parameters	2339/0/154
Goodness-of-fit on F^2	1.054
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0345$, $wR_2 = 0.0966$
Final R indexes [all data]	$R_1 = 0.0366$, $wR_2 = 0.0989$
Largest diff. peak/hole / e Å ⁻³	0.14/-0.45

Table S8. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{Å}^2 \times 10^3$) for compound **5a**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{11} tensor.

Atom	x	y	z	U(eq)
Cl1	7123.5(8)	10058.0(5)	6796.3(3)	60.76(15)
O1	1048.1(17)	3864.1(13)	2876.9(9)	48.4(2)
O2	-1032(2)	1677.4(15)	1614.2(11)	62.6(3)
N1	4350(2)	4090.6(14)	1928.9(11)	44.6(3)
N2	2741(2)	2826.9(15)	1313.9(11)	45.5(3)
N3	-1021(4)	3189(3)	-1138.8(19)	96.7(7)
C1	4181(2)	5991.4(16)	3807.6(12)	40.6(3)
C2	2816(3)	6508.7(18)	4740.5(13)	47.3(3)
C3	3710(3)	7754.6(19)	5666.4(13)	49.8(3)
C4	5980(3)	8488.9(17)	5640.1(12)	44.8(3)
C5	7375(3)	8001.6(19)	4716.7(14)	49.5(3)
C6	6487(2)	6748.9(19)	3807.4(13)	47.4(3)
C7	719(3)	2646.2(18)	1866.7(13)	47.9(3)
C8	3272(2)	4661.8(17)	2841.5(12)	41.4(3)
C9	3344(3)	1789.0(19)	246.1(14)	52.5(4)
C10	3129(3)	2522(2)	-809.2(15)	60.9(4)
C11	789(3)	2892(2)	-999.0(15)	64.1(4)

Table S9. Anisotropic Displacement Parameters ($\text{Å}^2 \times 10^3$) for compound **5a**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11} + 2hka^*b^*U_{12} + \dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	71.4(3)	53.9(2)	50.8(2)	2.41(16)	-8.06(18)	2.78(18)
O1	42.8(5)	52.2(6)	45.4(5)	5.8(4)	4.3(4)	-1.2(4)
O2	51.0(6)	64.1(7)	61.9(7)	2.1(5)	1.8(5)	-9.6(5)
N1	42.1(6)	41.9(6)	47.7(6)	6.0(5)	0.8(5)	4.9(5)
N2	44.3(6)	43.7(6)	45.1(6)	4.0(5)	1.8(5)	3.9(5)
N3	75.5(12)	129.5(19)	82.5(13)	9.1(12)	-18.7(10)	30.1(12)
C1	40.5(6)	40.3(7)	42.5(7)	11.9(5)	0.7(5)	6.4(5)
C2	42.9(7)	46.9(7)	51.2(8)	11.6(6)	7.6(6)	1.6(6)
C3	53.3(8)	48.9(8)	46.6(8)	9.7(6)	11.3(6)	6.1(6)
C4	51.3(8)	40.9(7)	42.4(7)	10.0(6)	-2.9(6)	6.9(6)
C5	38.8(7)	51.2(8)	56.2(8)	9.8(6)	0.1(6)	1.7(6)
C6	40.8(7)	52.1(8)	47.7(8)	7.7(6)	6.1(6)	6.2(6)
C7	46.7(7)	48.4(8)	46.4(7)	8.2(6)	0.6(6)	3.6(6)

C8	38.7(6)	41.4(7)	45.2(7)	12.0(5)	1.4(5)	5.6(5)
C9	48.4(8)	46.5(8)	57.2(9)	-2.9(6)	3.2(6)	11.3(6)
C10	51.2(8)	76.8(11)	48.6(8)	2.0(8)	8.0(6)	6.4(8)
C11	63.2(10)	78.0(12)	44.9(8)	0.8(8)	-4.3(7)	9.2(9)

Table S10. Bond Lengths for compound **5a**

Atom	Atom	Length/ \AA	Atom	Atom	Length/ \AA
C11	C4	1.7377(15)	C1	C2	1.387(2)
O1	C7	1.3892(18)	C1	C6	1.3966(19)
O1	C8	1.3722(16)	C1	C8	1.454(2)
O2	C7	1.2028(19)	C2	C3	1.383(2)
N1	N2	1.3840(17)	C3	C4	1.375(2)
N1	C8	1.2831(19)	C4	C5	1.384(2)
N2	C7	1.3485(19)	C5	C6	1.374(2)
N2	C9	1.4466(19)	C9	C10	1.515(2)
N3	C11	1.130(3)	C10	C11	1.458(3)

Table S11. Bond Angles for compound **5a**.

Atom	Atom	Atom	Angle/ $^\circ$	Atom	Atom	Atom	Angle/ $^\circ$
C8	O1	C7	105.71(11)	C5	C4	C11	119.32(12)
C8	N1	N2	103.69(11)	C6	C5	C4	119.50(13)
N1	N2	C9	121.09(12)	C5	C6	C1	120.17(14)
C7	N2	N1	112.38(12)	O2	C7	O1	124.32(14)
C7	N2	C9	126.37(13)	O2	C7	N2	131.19(15)
C2	C1	C6	119.18(13)	N2	C7	O1	104.49(12)
C2	C1	C8	121.34(13)	O1	C8	C1	119.20(12)
C6	C1	C8	119.47(13)	N1	C8	O1	113.73(13)
C3	C2	C1	120.92(13)	N1	C8	C1	127.05(13)
C4	C3	C2	118.73(14)	N2	C9	C10	112.78(13)
C3	C4	C11	119.19(12)	C11	C10	C9	113.07(14)
C3	C4	C5	121.49(14)	N3	C11	C10	179.5(2)

Table S12. Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for compound **5a**.

Atom	x	y	z	U(eq)
H2	1277	6011	4744	57
H3	2794	8089	6295	60
H5	8903	8518	4712	59
H6	7423	6404	3190	57
H9A	2326	754	120	63
H9B	4938	1584	329	63
H10A	4238	3513	-709	73
H10B	3538	1769	-1496	73

References

1. Sheldrick, G.M. (2015), *Acta Cryst.* A71, 3-8.
2. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst.* 42, 339-341.
3. Sheldrick, G.M. (2015), *Acta Cryst.* C71, 3-8.